#14

June 7 1993

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent No. 4,282,233

Inventors: Frank J. Villani and Charles V. Magatti

Attn: Box Patent Ext.

Issue Date: August 4, 1981

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Honorable Commissioner of Patents and Trademarks
Washington, D. C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. Sec. 156 and 37 C.F.R. Sec. 1.710-1.785, Schering Corporation, owner of the above-identified patent by (1) an Assignment by Frank J. Vallani of his interest on June 17, 1980 (Exhibit X), recorded in the U. S. Patent and Trademark Office ("USPTO") on August 25, 1988 at Reel: 3792, Frame: 0905 and (2) an Assignment by Charles V. Magatti of his interest on October 31, 1990 (Exhibit XI); recorded in the USPTO on November 8, 1990 at Reel: 5509, Frame: 0030, hereby requests an extension of the patent term of United States Patent No. 4,282,233. The following information is submitted in accordance with 35 U.S.C. Sec. 156(d) and the rules for extension of patent term issued by the Patent and Trademark Office at 37 C.F.R. Subpart F, Sec.1.710 to 1.785 and follows the numerical format set forth in 37 C.F.R. Sec.1.740:

(1) A complete identification of the approved product as by appropriate chemical and generic names, physical structure or characteristics:

The approved product is CLARITIN® (brand of loratadine) tablets; the active ingredient in the approved product has the following chemical names:

1. Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclophepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate (USAN).

2. 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-,ethyl ester (CAS).

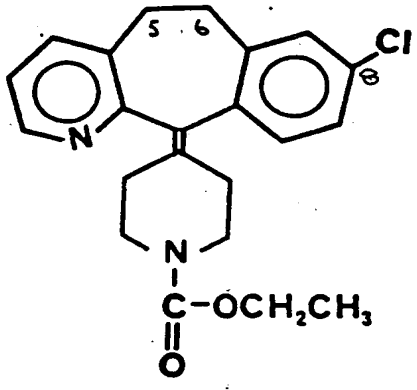
3. 8-Chloro-6,11-dihydro-11-(1-ethoxy-carbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

4. 11-[N-(Ethoxycarbonyl)-4-piperidylidene]-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclophepta[1,2-b]pyridine; .(The Merck Index 11 Edition (1989) page 877, Cite #5455) and

5. 11-(N-Carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]pyridine (The compound of Example 1B of United States Patent No. 4,282,233).

and the following generic name: Loratadine, SCH Compound No.29851.

and is represented by the following structural formula:



11-[N-(Carboethoxy-4-piperidylidene]-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine is the active ingredient in the product CLARITIN® (brand of loratadine) tablets as may be seen from paragraph A-l(a) on page 1 of the attached Exhibit I, entitled, "Description Including Physical and Chemical Characteristics and Stability" which was submitted to the FDA with the NDA #19-658 for the approved product.

(2). A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S. Sec. 301 et seq. Section 505(b) provides for the submission and approval of new drug applications ("NDAs") for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3). An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

CLARITIN® (brand of loratadine) tablets was approved by the Food and Drug Administration ("FDA") for commercial marketing on April 12, 1993. (See Exhibit VII).

(4). In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that is has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, ("FFDCA"), the Public Health Service Act or the Virus-Serum Toxin Act or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The active ingredient in the approved product, CLARITIN® (brand of loratadine) tablets, has the generic name of loratadine and the chemical names listed in paragraph no. (l) hereinabove as well as in paragraph A-l(a) on page 1 of Exhibit I. The approved product CLARITIN® (brand of loratadine) tablets contains loratadine as the sole active ingredient which active ingredient has not been previously approved for commercial marketing or use under FFDCA. The FDA has approved CLARITIN® (brand of loratadine) tablets for relief of nasal and non-nasal symptoms of seasonal allergic rhinitis. CLARITIN® (brand of loratadine) tablets was approved by the FDA under Section 505(b) of FFDCA. (See Exhibit VII).

(5). A statement that the application is being submitted within the sixty day period permitted for submission pursuant to Sec. 1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on April 12, 1993 and the last day within the sixty day period permitted for submission of an application for extension of the relevant U. S. Patent is June 11, 1993. This application is being timely filed before the June 11, 1993 deadline..

(6). A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, and the date of issue:

United States Patent No. 4,282,233
Inventors: Frank J. Villani and Charles V. Magatti
Date of Issue: August 4, 1981
Date of Expiration: August 4, 1998 (before extension)

(7). A copy of the patent for which an extension is being sought including the entire specification (including claims), and drawings:

A copy of the patent is attached as Exhibit II.

(8). A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certif issued in the patent:

Two Certificates of Correction (Exhibits VIII and IX, attached hereto) have been issued by the USPTO:

A. Certificate of Correction (Exhibit VIII) signed and sealed November 24, 1981 changed the spelling of Inventor "Frank J. Vilani" to--Frank J. Villani--.

B. Certificate of Correction of Inventorship (Exhibit IX) signed and sealed December 26, 1989 was issued pursuant to submission and acceptance of a petition

requesting a Certificate of Correction of inventorship pursuant to 35 USC Sec. 256. The USPTO found that United States Patent No. 4,282,233 through error and without deception, improperly set forth the inventorship. The correct inventorship of United States Patent No. 4,282,233 is Frank J. Villani and Charles V. Magatti (See Exhibit IX).

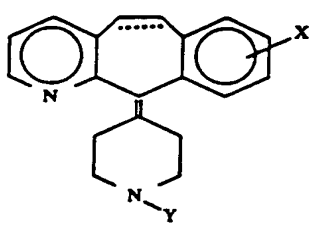
Note that United States Patent No. 4,282,233 is based on an Application Serial No. 160,795, filed June 19, 1980 and as such is <u>not</u> subject to the payment of maintenance fees pursuant to 35 USC Sec. 41(b)(1).

United States Patent No. 4,282,233 has not been re-examined and as such no re-examination certificate has been issued.

(9). A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

United States Patent No. 4,282,233 issued with 13 claims.

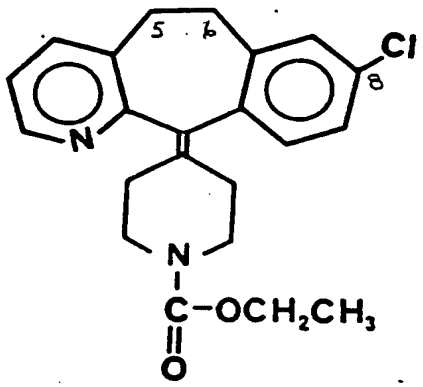
Claim 1 reads: A compound of the formula



(I)

wherein the dotted line represents an optional double bond; X is hydrogen or halo; and wherein Y is-COOR or SO_2R; with the proviso that when Y is-COOR, R is C_1 to C_{12} alkyl, substituted C_1 to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} phenylalkyl wherein the phenyl moiety is substituted or R is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substitutents on said substituted C_1 to C_{12} alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C_1 to C_6 alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C_7 to C_{12} phenylalkyl are selected from C_1 to C_6 alkyl and halo, and the substituent on said N-substituted piperidyl is C_1 to C_4 alkyl; and with the proviso that when Y is SO_2R, R is C_1 to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} phenylalkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C_7 to C_{12} phenylalkyl are slected from C_1 to C_6 alkyl and halo.

The structural formula for loratadine is set forth on page 1 of Exhibit I and paragraph (l) herein above is



Thus, claim 1 covers loratadine wherein there is a single bond between the 5-and 6-carbons, X is halo and Y is COOR and R is C_1 to C_{12} alkyl; in loratadine X is chloro which is a halo atom and R is ethyl which is a C_1-C_{12} alkyl group.

Claim 2 reads: A compound according to claim 1, wherein Y is -COOR, wherein R is as defined in claim 1, said compound having a single bond between the 5- and 6-positions of formula I of claim 1.

and covers loratadine for the reasons set forth in reference to claim 1

Claim 5 reads: A compound according to claim 2, wherein X is 8-chloro, said compound having a single bond between the 5- and 6-carbons

and covers loratadine for the reasons set forth in reference to claims 1 and 2.

Thus, Claims 1, 2 and 5 <u>generically</u> cover loratadine as the compound <u>per se.</u>

Claim 7 directed to the specific compound, 11-(N-carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine, <u>specifically</u> covers loratadine as the compound <u>per se</u>. (See paragraph (l) hereinabove).

Claim 12, directed to an antihistaminic pharmaceutical composition comprising an effective amount of a compound as claimed in any one of claims 1 to 10 and a pharmaceutically acceptable carrier, covers loratadine drug product composition approved by the FDA (see Exhibit I, page 3 for the approved loratadine pharmaceutical composition and see the heading for package insert--Exhibit XII on page 1 whereat it is stated that CLARITIN® (brand of loratadine) tablets is a long-acting <u>antihistimine</u>.

Claim 13, directed to a method of effecting an anti-allergic response in an animal comprising administering to the animal an effective amount of a compound as claimed in any one of claims 1 to 11. CLARITIN® (brand of loratadine) tablets the approved drug product was approved by the FDA in a letter dated April 12, 1993 (Exhibit VII) to be "safe and effective for relief of nasal and non-nasal symptoms of seasonal <u>allergic</u> rhinitis".

The approved drug is disclosed in United States Patent No. 4,282,233 in Example 1B at column 3, lines 5 to 12. The approved indication for the approved drug United States Patent No. 4,282,233 is disclosed at column 4, lines 42-46:

> "The compounds of the present invention are useful as non-sedating antihistamines. These compounds act as anti-allergic agents in the treatment of such conditions as perennial and seasonal allergic rhinitis and chronic urticaria" (emphasis added).

Thus, the approved drug and the approved indication and usage of the approved drug are embraced by claims 1, 2, 5, 7 12 and 13 of United States Patent No. 4,282,233.

(10) A statement beginning on a new page, of the relevant dates and informaton pursuant to 35 U.S.C. Sec. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a new drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued:

Schering Corporation ("Schering") of Kenilworth, New Jersey, is the assignee of record of United States Patent No. 4,282,233 by virtue of (1) the Assignment by Frank J. Villani of his interest in United States Patent No. 4,282,233 (Exhibit X) recorded in the USPTO at Reel: 3792, Frame: 0905 and (2) the Assignment by Charles V. Magatti of his interest in United States Patent No. 4,282,233 (Exhibit XI) recorded in the USPTO at Reel: 5509 and Frame: 0030.

In furtherance of the need for an approved NDA, Schering, on November 30, 1982, submitted to the FDA, a "Notice of Claimed Investigational Exemption for a New Drug" (hereinafter referred to as an "IND") under Section 505(i) of the FFDCA for the purposes of conducting clinical studies to support the approval of a subsequent NDA for SCH 29851 (loratadine) a non-sedating antihistamine in the form of

oral capsules. Thereafter the loratadine capsule IND was amended by the filing of a loratadine tablet formulation. A copy of the Schering letter transmitting the IND to the FDA is attached as Exhibit III. By a letter dated January 6, 1983, the FDA acknowledged the date of receipt of the IND as December 7, 1982, assigned the IND Number 21,249, and indicated that the IND study may be initiated 30 days after the date of receipt, i.e., on January 6, 1983. A copy of this FDA letter is attached as Exhibit IV. This establishes the beginning of the "regulatory review period" under 35 U.S.C. Section 156(g)(1) as January 6, 1983, the effective date of an Investigational exemption under Section 505(i).

Schering submitted a NDA for CLARITIN® (brand of loratadine tablets, NDA #19-658, on October 31, 1986. A copy of the Schering letter dated October 31, `1986, transmitting the above-disclosed NDA is attached hereto as Exhibit V. By a letter dated November 5, 1986 the FDA acknowledged the date of receipt of NDA #19-658 for loratadine tablets as October 31, 1986 and indicated the effective filing date will be December 31, 1986.

Thus, for purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. Section 156(g)(1)(B)(i), the "testing phase" began on January 6, 1983, the date of the exemption under subsection (i) of Sec. 505 became effective and ended on October 31, 1986, the date the NDA #19-658 was initially submitted by Schering for loratadine tablets under Section 505(b) of the FFDCA. And, for purposes of determining the "approval phase of the "regulatory review period" under 35 USC Sec. 156(g)(1)(B)(ii) the "approval phase" began on October 31, 1986, the date the NDA #19-658 for loratadine tablets was intially submitted by Schering to the FDA and ended on April 12, 1993, the date NDA #19-658 was approved by the FDA.

(11). A brief description of the activities undertaken by Schering, the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Schering, the marketing applicant, was actively involved in obtaining FDA

approval for CLARITIN® (brand of loratadine) tablets. As previously noted Schering submitted an IND for loratadine capsules on November 30, 1982 and in close consultation with the FDA, subsequently conducted clinical trials in 1983 under IND #21,249 for loratadine. Loratadine progressed through various phases of clinical trials until an NDA for CLARITIN® (brand of loratadine) tablets was filed on October 31, 1986. Schering had used loratadine capsules in the Phase I (pharmacokinetic studies) and started using loratadine tablets in the Phase II clinical studies. (Note that the CLARITIN® trademark was not used until December 21, 1987 and earlier communications with the FDA did not use the CLARITIN® trademark). In October, 1987, CLARITIN® (brand of loratadine) tablets were recommended for approval by the FDA's Pulmonary-Allergy Advisory Committee. Schering thereafter worked with the FDA and attempted to establish the bioequivalency of capsules and tablets as well as the safety and efficacy of the loratadine tablets. In August, 1988 a summary of loratadine tablet/capsule bioequivalency studies was submitted to the FDA and a large scale, multicenter clinical therapeutic equivalence study was initiated to compare loratadine tablets vs. loratadine capsules vs. placebo in treating seasonal allergic rhinitis. Schering submitted the results of this clinical therapeutic equivalence study to the FDA in November, 1988. (Note that seasonal allergeric rhinitis is the FDA-approved indication for loratadine tablets). In December, 1988, the FDA questioned the bioequivalency of loratadine in the capsule form used for Phase I studies and the tablet formulation that would eventually be marketed; the FDA questioned the validity of the statistical methodology used in this study as well as the validation of the assay method used to measure the loratadine blood levels. During the latter part of 1989 and throughout 1990, Schering continued to work with the FDA to progress the loratadine NDA. In 1990, the FDA presented to Schering many new issues including the issue of the very nature of non-sedating antihistamines as a class; the issues were thoroughly addressed by the Schering medical and regulatory staffs. Starting in November, 1989 the FDA raised questions regarding the carcinogenicity data submitted to the loratadine NDA as well as the carcinogenicity potential of sedating and non-sedating antihistamines and such questions resulted in a Pulmonary and Allergy Drug Products Advisory Committee meeting in June, 1991. At this June, 1991 Advisory Committee Meeting, the Schering toxicology data on CLARITIN® (brand of loratadine) tablets were presented and discussed. The Advisory Committee reviewed the data on animal adenomas and ruled that CLARITIN® (brand of loratadine) tablets were unlikely to pose an undue risk to humans. During the rest of 1991, and throughout 1992 and early

1993, (until the NDA was approved on April 12, 1993) Schering regulatory and medical representatives continued to interact with various FDA officials and answer numerous questions, generate requested data and supply requested information regarding inter alia carcinogenicity, package inserts, advertising issues as well as all clinical studies and data on loratadine submitted worldwide to obtain health approval. A brief description of the significant activities undertaken by Schering with respect to CLARITIN® (brand of loratadine) tablets during the regulatory review period is set forth in Exhibit XIII and is illustrative of the activities involved.

(12). A statement that in the opinion of the applicant that the patent is eligible for an extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C . Sec. 156(a):

Section 156(a) provides, in the relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an applicaton for extension is submitted; (2) the term of the patent has never been extended; (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. Sec. 156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of United States Patent No. 4,282,233 expires on August 4, 1998. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 4,282,233.

(2) The term of this patent has never been extended.

(3) This application is being submitted by the owner of record, Schering Corporation by virtue of the two Assignments: one Assignment by Frank J. Villani of his interest was recorded in the U. S. Patent and Trademark Office on August 25, 1988, at Reel: 3792, Frame: 0905, (copy attached as Exhibit X) and a second Assignment by Charles V. Magatti of his interest was recorded in the U. S. Patent and Trademark Office on October 31, 1990 at Reel: 5509, Frame: 0030; (copy attached as Exhibit XII). This application is submitted in accordance with 35 U. S. C. Sec. 156(d) in that it is submitted within the sixty-day period beginning on the date, April 12, 1993, the product received permission for marketing under the Federal Food, Drug and Cosmetics Act and ending on the date June 11, 1993 and contains the information required under 35 U.S.C. Sec. 156(d).

(4) As evidenced by the April 12, 1993 letter from the FDA (Exhibit VII), the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

5. Finally, CLARITIN® (brand of loratadine) tablets were approved by the FDA for relief of nasal and non-nasal symptoms of seasonal allergic rhinitis. The permission for the commercial marketing of CLARITIN® (brand of loratadine) tablets after regulatory review under Section 505(b) is the first permitted commercial marketing of the active ingredient in CLARITIN® (brand of loratadine) tablets. This is confirmed by the absence of any approved new drug application for the active ingredient prior to April 12, 1993.

(b) Statement as to length of extension claimed:

The term of United States Patent No. 4,282,233 should be extended by two years (731 days) to August 4, 2000. This extension was determined on the following basis. As set forth in 35 U.S.C. Sec. 156(g)(1), the regulatory review period equals the length of time between the effective date of the initial IND #21,249 (January 6, 1983) and the initial submission of the NDA #19-658 (October 31, 1986), a

period of 1,395 days, plus the length of time between the initial submission of the NDA #19-658 (October 31, 1986) to NDA approval (April 12, 1993), a period of 2,356 days. These two periods added together equal 3,751 days.

Pursuant to 35 U. S. C. Sec. 156(c), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent is issued. In this case Sec. 156(c) does not apply in that the issue date of United States Patent No. 4,282,233, August 4, 1981, is before the January 6, 1983 date on which the regulatory review period began.

The calculation made pursuant to Sec. 156(c)(2), requires the above period to be reduced by one-half of 1,395 day period; this calculation results in a value of 698 days.

From the foregoing calculation, an extension of 3053 days, that is, some 8 years thereby results. However, pursuant to 35 U. S. C. Sec. 156(g)(4)(c), the period of extension determined under any of the preceding paragraphs may not exceed two years (1) if the patent involved was issued before the date of enactment of this section; and (2) if an action described in subparagraph (b) was taken before the date of enactment of this section with respect to the approved product; and (3) if the commercial marketing or use of the product has not been approved before such date.

As discussed below by the corresponding number, each of the elements of 35 U.S.C. Sec. 156(g)(4)(c) applies:

(1) The instant patent, United States Patent No. 4,282,233, was issued on August 4, 1981, which is a date before September 24, 1984, the date of enactment of 35 U. S. C. Sec. 156(g)(4)(C); (2) an IND for the drug was submitted on November 30, 1982 and having an effective date of January 6, 1983 which is a date before the date of enactment of the relevant section; and (3) the commercial marketing or use for the drug was approved on April 12, 1993 which is a date after the date of enactment of the relevant section.

Since the period of extension for the involved patent determined under 35 U. S. C. Sec. 156(c) is equal to the sum of 698 days plus 2356 days or 3,054 days, which is greater than 2 years (731 days),

the term of the involved patent is eligible for a 731 day extension under 35 U. S. C. Sec. 156(g)(4)(C), that is, until August 4, 2000.

Pursuant to Section 156(c)(3), if the period remaining in the term of the patent after the date of approval, that is, (April 12, 1993 to August 4, 1998 (representing a period of 1,940 days) when added to the period of extension determined under 35 U. S. C. Section 156(g)(4)(c) (that is a period of 731 days) exceeds 14 years (5,113 days), the period of extension must be reduced so that the total of both such periods does not exceed fourteen years. In this case, the total of both such periods is 2,671 days which is less than 5,113 days, i.e. 14 years and accordingly 35 USC Sec. 156(c)(3) is not applicable.

Accordingly, the term of the patent is eligible for a 731 day extension until August 4, 2000.

(13). Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to the appliction for extension. Further to the information already presented in this application and the attached Exhibits, Applicant notes that the inventorship of instant United States Patent No. 4,282,233 was corrected pursuant to 35 U. S. C. 256 by the filing of the appropriate Petitions, Declarations by Frank J. Villani, and Charles V. Magatti and by the appropriate official for the assignee of record.

In the Certificate of Correction signed and sealed on December 6, 1989, the USPTO acknowledged that "On petition requesting issuance of a certificate of correction of inventorship pursuant to 35 U. S. C. 256, it has been found that the above-identified patent, through error and without any deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is: Frank J. Villani and Charles V. Magatti" (See Exhibit IX).

As stated in paragraph no. (9) hereinabove, claims 1, 2, 5, 7, 12 and 13 of the instant United States Patent No. 4,282,233 embrace the approved product, CLARITIN® (brand of loratadine) tablets and the approved indication and usage of said approved product.

The term of United States Patent No. 4,282,233 has never been extended. A copy of this patent is attached as Exhibit II.

(14). Prescribed fees:

The Commissioner is authorized to charge our Deposit Account No. 19-0365 in the amount of $1,000.00 or any other fee necessary for this application to prevent it from becoming inadvertently abandoned.

(15). The name, address and telephone number of the person to whom inquiries and correspondence relating to this application for patent term extension are to be directed to:

Thomas D. Hoffman
Schering-Plough Corporation
Patent Department, 3-West
One Giralda Farms
Madison, New Jersey 07940-1000
Tel. No. (201) 822-7379

(16). Certification that the enclosed duplicate copy of this application is a true copy of the original:

DECLARATION FOR EXTENSION OF UNITED STATES PATENT NO. 4,282,233

I, Thomas D. Hoffman, Registration No. 28,221, as duly appointed attorney for Applicant, Schering Corporation, the owner of record of United States Patent No. 4,282,233 (by virtue of the aforesaid Assignments, Exhibits X and XI)) which has applied for an extension of term of this patent, declare that I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,282,233; that I believe that the patent is subject to extension under 35 U. S. C. Sec. 156; that I believe that the length of extension claimed is fully justified under 35 U. S. C. Sec. 156, and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U. S. C. Sec. 156. I certify that the duplicate copy of this applicaton transmitted herewith is a true copy of the original applicaton.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements mfay jeopardize the validity of this application and any extension of United States Patent No. 4,282,233.

Date: 6/4/93

Thomas D Hoffman

Thomas D. Hoffman
Attorney for Assignee of Record
Reg. No. 28,221
Tel. No. (201) 822-7379

17. DECLARATION AND POWER OF ATTORNEY BY OWNER OF RECORD

As the below identified official of Schering Corporation, the owner of record of United States Patent No. 4,282,233, which has applied for an extension of term of this patent, I declare (1) that I have been authorized to obligate Schering Corporation and I am a patent agent authorized to practice before the Patent and Trademark Office and have authority from the owner of record to act on behalf of the owner of record in patent matters; (2) that I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,282,233; (3) that I believe that the patent is subject to extension under 35 U.S.C. Sec. 156 and 37 C.F.R. Sec. 1.710; (4) that I believe that the length of extension claimed is fully justified under 35 U.S.C. Sec. 156 and the applicable regulations; and (5) that I believe that the patent for which an extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. Sec. 156 and 37 C. F. R. Sec. 1.720.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and United States Patent No. 4,282,233.

POWER OF ATTORNEY: I hereby appoint as United States attorneys and with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Thomas D. Hoffman Registration No. 28,221; John J. Maitner, Registraton No. 25,636; Norman C. Dulak, Registration No. 31608; Edward H. Mazer, Registration No. 27,573; James R. Nelson, Registration No. 27929 and Eric S. Dicker, Registration No. 31,699.

Send correspondence to:

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Date: 6.4.93

By: S. Kanstad

Dr. Steinar V. Kanstad,
Staff Vice President - Patents
Schering-Plough Corporation
Reg. No.: 31700

EXHIBIT I

A-1. Description including physical and chemical characteristics and stability.

Loratadine is a new entity, nonsedating antihistamine. A summary of pertinent information is provided in this section.

(a) Nomenclature and Code Designations

Generic name: Loratadine

Code designation: Sch 29851

CAS registry number: CAS-79794-75-5

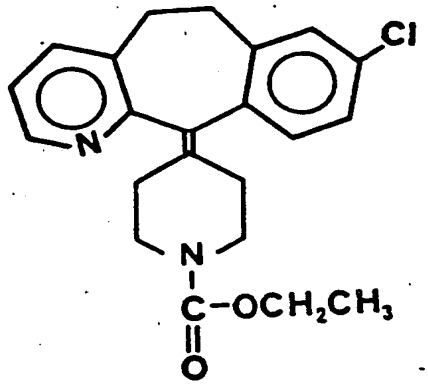
Chemical names:

(a) Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate (USAN)

(b) 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-, ethyl ester (CAS)

(c) 8-Chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine

(b) Structure



Empirical formula: $C_{22}H_{23}N_2ClO_2$

Molecular weight: 382.9

(c) Physical and Chemical Characteristics

Appearance:	White to off-white powder
Solubility:	Insoluble in water, freely soluble in acetone, chloroform, methanol, and toluene
Melting range:	131° to 137°C
pH:	not applicable
pKa:	5.0
Polymorphism:	A single polymorph as evidenced by solid state infrared spectroscopy and powder X-ray diffraction.

B-2

DRUG PRODUCT COMPOSITION

	mg/tablets
Loratadine Micronized	10
Corn Starch (Food Grade)	18
Lactose Hydrous NF	71
Magnesium Stearate NF	1*
Water Purified USP (Evaporates)	--
Approx. Tablet Weight	100

*May vary from 0.7 to 2 mg/tablet with compensating adjustments made in the tablet weight or the amount of lactose, or both.

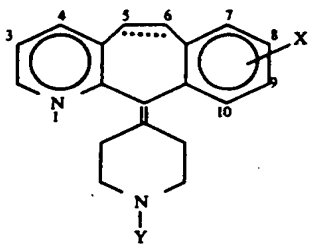
ANTIHISTAMINIC 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2-B]-PYRIDINES

The present invention relates to novel 11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines.

U.S. Pat. No. 3,326,924 discloses 6,11--dihydro-11-(N-methyl-4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine and 11-(N-methyl-4-piperidylidene-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine, useful as antihistamines.

The compounds of the present invention are likewise useful as antihistamines, but are preferred to the compounds of the aforementioned patent because the present compounds have little or no sedative effects, thus being preferred for use with patients that must operate machinery or automobiles or perform other mental or physical tasks requiring a high level of concentration.

The compounds of the present invention are compounds of the formula



(I)

wherein the dotted line represents an optional double bond and wherein the numbering system used herein is illustrated. In this formula, X is hydrogen or halo and Y is substituted carboxylate or substituted sulfonyl for example Y is —COOR or SO_2R, with the proviso that when Y is —COOR, R is C_1 to C_{12} alkyl, substituted $C_1$to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenyl alkyl, C_7 to C_{12} phenyl alkyl wherein the phenyl moiety is substituted or R is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substituents on said substituted C_1 to C_{12} alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C_1 to C_6 alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C_7 to C_{12} phenyl alkyl are selected from C_1 to C_6 alkyl and halo, and the substituent on said N-substituted piperidyl is C_1 to C_4 alkyl; and with the proviso that when Y is SO_2R, R is C_1 to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenyl alkyl, C_7 to C_{12} phenyl alkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C_7 to C_{12} phenyl alkyl are selected from C_1 to C_6 alkyl and halo.

In a preferred embodiment of the present invention, Y is —COOR and R is C_1 to C_6 alkyl or substituted alkyl, phenyl, substituted phenyl, C_7 to C_{12} aralkyl or substituted aralkyl or -2, -3 or -4 piperidyl or N-substituted piperidyl. When R is substituted alkyl, R is substituted with amino or with substituted amino. The substituents on said substituted amino are C_1 to C_6 alkyl. The substituents on the aforementioned substituted

phenyl and on the phenyl moiety of the substituted aralkyl are preferably C_1 to C_6 alkyl or halo.

In a second preferred embodiment of the present invention, Y is SO_2R and R is C_1 to C_6 alkyl, phenyl, substituted phenyl, C_7 to C_{12} aralkyl or substituted aralkyl, wherein the substituents on said substituted phenyl and on the phenyl moiety of the substituted aralkyl are C_1 to C_6 alkyl or halo.

The aforementioned alkyl groups may be linear, branched or cyclic or may contain both cyclic and linear or cyclic and branched moieties. Halo may be fluoro, chloro, bromo or iodo.

The present invention also relates to a pharmaceutical composition comprising an effective amount of a compound of the formula I as defined above, together with a pharmaceutically acceptable carrier and to a method of effecting an anti-allergic response in an animal comprising administering to the animal an effective amount of a compound of the formula I as defined above.

Generally, compounds of the present invention are prepared by replacing a methyl or another replacable substituent, for example carbophenoxy on the nitrogen of the piperidylidene ring of an appropriate compound of the formula I with the desired substituent.

For example, compounds of the formula I wherein Y is —COOR are prepared by reacting a compound of the formula I wherein Y is methyl (Compound IA) or an appropriate derivative of Compound IA with an appropriate chloroformate, for example, an alkylchloroformate or phenyl chloroformate in order to replace the N-methyl group on the piperidylidene group of Compound IA.

Compounds of the formula I wherein Y is —COOR may also be prepared by reacting a compound of the formula I wherein Y is —COOR and R is phenyl with the sodium salt of an appropriate alcohol.

Compounds of the formula I wherein Y is —COOR and R is tert-butyl may be prepared by reacting a compound of the formula I wherein Y is hydrogen with a di-tertiarybutyl carbonate in an inert solvent, for example, tetrahydrofuran.

Compounds of the formula I wherein Y is —SO_2R are prepared by reacting a compound of the formula I wherein Y is hydrogen with a compound of the formula Cl—SO_2R, wherein R has the same value as R in the desired product, in the presence of an excess of anhydrous potassium carbonate in an inert solvent, for example dry toluene.

The following non-limiting Examples further illustrate the preparation of the compounds of the present invention:

EXAMPLE 1

A.

11-(N-Carboethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine

To a solution of 10.9 g (0.1 mole) of ethylchloroformate in 300 ml. of anhydrous benzene is added dropwise, with stirring at room temperature, a solution of 14.5 g (0.05 M) of 11-(N-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IA) in 200 ml of benzene. The solution is stirred and is heated under reflux overnight (16–20 hrs.). The mixture is cooled and is poured into ice water and the organic layer is separated, washed with water, dried, and then concentrated to dryness. The residue is triturated with petroleum ether and a white solid having

a melting point of 106°–107° C. is recrystallized from isopropyl ether after decolorization with decolorizing carbon.

B.

11-(N-Carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine

Using the procedure of Example IA, react 16.2 g of the 8-chloro derivative of Compound IA and 10.9 g (0.1 mole) of ethylchloroformate to prepare the title compound, having a melting point of 128°–130° C. The 7,9 and 10-chloro analogues are similarly prepared.

C.

11-(N-Carbomethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine

Using the procedure of Example IA, react 14.5 g of Compound IA and 9.4 g of methylchloroformate to prepare the title compound, having a melting point of 116°–118° C.

EXAMPLE 2

11-(N-Carbophenoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IB)

To a solution of 29.1 g (0.1 mole) of Compound IA in 150 ml. of anhydrous carbon tetrachloride is added 17 g of phenylchloroformate in an equal volume of anhydrous carbontetrachloride. Heat under reflux for 15 minutes with stirring and pour into water. Separate and wash the organic layer with water and remove solvent. Extract the residue with ether, filter off the insoluble material and remove the ether. The residue is recrystallized from isopropyl ether to yield the title compound having a melting point of 127°–130° C.

Similarly prepare the 7,8,9, or 10-chloro derivatives of the title compound using this procedure:

EXAMPLE 3

11-(N-Carboisopropoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b] pyridine

Dissolve 0.5 g sodium metal in 50 ml isopropanol and add 7.9 g of Compound IB from Example 2. Heat with stirring for 5 hours on the steam bath at 90°–95° and allow to cool overnight.

Add ice water to precipitate the product and extract 3 times with ether and once with chloroform. Wash with water, distill off solvents, triturate with hexane and recrystallize from isopropylether. The melting point is 147°–148° C.

Using this procedure and replacing the isopropanol with n-butanol, cyclopentanol, allylalcohol, cyclopropylmethanol, benzylalcohol, p-chlorobenzylalcohol, phenethylalcohol, dimethylaminoethylalcohol or N-methyl-4-hydroxy piperidine prepare the corresponding carbamoyl derivatives. Similarly, using the chloro derivatives of Compound IB and the sodium salts of the aforementioned alcohols, prepare the chloro derivatives of the aforementioned carbamoyl derivatives.

EXAMPLE 4

11-(N-Carbo-t-butoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

Dissolve 13.8 g of 11-(4-piperidylidene)-6,11 dihydro-5H-benzo-[5,6]-cycloheptа-[1,2-b]-pyridine (Compound IC) prepared according to Villani et. al., J. Med. Chem. 15, 750 (1972) in 250 ml of dry tetrahydrofuran. With stirring, add in one portion 12 g of di-t-butyl carbonate and stir at room temperature overnight. The mixture is poured into water, is extracted with ether, is washed with water and the solvent removed. Recrystallize the residue from isopropyl ether. The melting point is 144°–145° C.

EXAMPLE 5

11-(N-Methanesulfonyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

To 10 g of Compound IC in 200 ml of dry toluene add 13 g of anhydrous potassium carbonate. After several minutes of stirring at room temperature, add dropwise a solution of 6 g of methanesulfonyl chloride in 20 ml of toluene. Continue stirring for 16 to 20 hours and then filter. Recrystallize the solid material from ethanol. The melting point is 223°–224° C.

Using this procedure and adjusting the weight of the requisite sulfonyl chloride so that 0.04 moles of said alkanesulfonyl chloride are used, the ethanesulfonyl, n-propylsulfonyl, n-butylsulfonyl, cyclopropylsulfonyl, heptylsulfonyl, dodecylsulfonyl, phenylsulfonyl, p-methylphenyl-sulfonyl, p-fluorophenylsulfonyl, p-chlorophenylsulfonyl, benzylsulfonyl, p-chlorobenzyl-sulfonyl, p-tertbutylphenylsulfonyl and cyclopentylsulfonyl compounds of formula I wherein Y is SO_2R are obtained.

Similarly, prepare the tricyclic ring substituted chloro derivatives.

Substituting the appropriate starting material having a double bond between the 5 and 6 positions of the ring system, and using the procedures set forth in Examples 1 to 5 above for the corresponding 6,11-dihydro compounds, the corresponding 6,11-dehydro compounds are prepared. Also, by substituting the appropriate bromo or other halo analogue, as desired, of the chloro compounds of the Formula I used as starting materials, the desired halo compounds of the formula I are prepared.

The compounds of the present invention are useful as non-sedating antihistamines. These compounds act as anti-allergic agents in the treatment of such conditions as perennial and seasonal allergic rhinitis and chronic urticaria.

The compounds of the present invention are administered in pharmaceutical formulations comprising the compound in admixture with a pharmaceutical carrier suitable for enteral or parenteral administration. The formulations may be in solid form, as for example tablets and capsules, or in liquid form as for example syrups, elixirs, emulsions, and injectables. In the formulation of pharmaceutical dosage forms there generally is utilized excipients as for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, and petroleum jelly. Preferred formulations are more fully illustrated in Example 6.

Although the required dosage will be determined by such factors as the patient's age, sex, weight and the severity of the allergic reaction to be treated, the preferred human dosage range is likely to be 4 to 50 mg of the effective compound 1 to 3 times per day. The preferred dosage ranges for other animals can readily be determined by using standard testing methods.

The following Examples are illustrative of the aforementioned pharmaceutical compositions:

EXAMPLE 6

A syrup comprising a compound of the present invention (Active Compound) is prepared from the following ingredients:

	per ml
Active Compound	0.100 mg
Sucrose	600 mg
Sorbitol	140 mg
Propylene Glycol	20.0 mg
Methylparaben	1.00 mg
Propylparaben	0.200 mg
F.D. & C. Yellow No. 6	0.225 mg
Alcohol USP	0.0021 ml
Limitation Black Currant Flavor	0.001 ml
Purified Water USP	q.s.
	1.0 ml

The syrup is prepared by combining the above ingredients according to standard techniques.

EXAMPLE 7

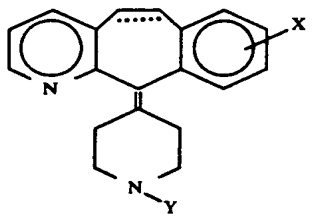
A tablet comprising a compound of the present invention (Active Compound) is prepared by a spray-dry process from the following ingredients:

Component I	mg/tablet
Active Compound	1.00
Lactose, Hydrous USP (Impalpable Powder)	212
Polyvinylpyrrolidine Povidone NF	10.0
Corn Starch (Food Grade)	15.0
Purified Water USP (Evaporates)	0.102 ml
Additional Components	
Corn Starch (Food Grade)	11.5
Magnesium Stearate USP	0.500

The materials of Component I are combined and spray dried by standard techniques. The resulting spray dried material is combined with the additional components listed above and processed to form tablets.

I claim:

1. A compound of the formula



(I)

wherein the dotted line represents an optional double bond; X is hydrogen or halo; and wherein Y is —COOR or SO_2R; with the proviso that when Y is —COOR, R is C_1 to C_{12} alkyl, substituted C_1 to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} phenylalkyl wherein the phenyl moiety is substituted or R is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substituents on said substituted C_1 to C_{12} alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C_1 to C_6 alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C_7 to C_{12} phenylalkyl are selected from C_1 to C_6 alkyl and halo, and the substituent on said N-substituted piperidyl is C_1 to C_4 alkyl; and with the proviso that when Y is SO_2R, R is C_1 to C_{12} alkyl, phenyl, substituted phenyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} phenylalkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C_7 to C_{12} phenylalkyl are selected from C_1 to C_6 alkyl and halo.

2. A compound according to claim 1, wherein Y is —COOR, wherein R is as defined in claim 1, said compound having a single bond between the 5- and 6-carbons.

3. A compound according to claim 1, wherein Y is —SO_2R, wherein R is as defined in claim 1, said compound having a single bond between the 5- and 6-carbons.

4. A compound according to claim 2, wherein X is hydrogen, said compound having a single bond between the 5- and 6-carbons.

5. A compound according to claim 2, wherein X is 8-chloro, said compound having a single bond between the 5- and 6-carbons.

6. A compound according to claim 3, wherein X is hydrogen, said compound having a single bond between the 5- and 6-carbons.

7. 11-(N-carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

8. 11-(N-methanesulfonyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

9. 11-(N-carboethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

10. 11-(N-carbomethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

11. 11-(N-carbophenoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

12. An antihistaminic pharmaceutical composition comprising an effective amount of a compound as claimed in any one of claims 1–10 and a pharmaceutically acceptable carrier.

13. A method of effecting an anti-allergic response in an animal comprising administering to the animal an effective amount of a compound as claimed in any one of claims 1 to 11.

* * * * *

EXHIBIT II

United States Patent [19]

Vilani

[11] **4,282,233**

[45] **Aug. 4, 1981**

[54] **ANTIHISTAMINIC 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2-B]-PYRIDINES**

[75] Inventor: **Frank J. Vilani**, West Caldwell, N.J.

[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[21] Appl. No.: **160,795**

[22] Filed: **Jun. 19, 1980**

[51] **Int. Cl.**[3] **A61K 31/445**; C07D 401/04

[52] **U.S. Cl.** **424/267**; 546/93

[58] **Field of Search** 546/93; 424/267

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,326,924	6/1967	Villani	546/93
3,357,986	12/1967	Villani	546/93
3,366,635	1/1968	Villani	546/93
3,419,565	12/1968	Villani	546/93

OTHER PUBLICATIONS

Villani, F., et al., *J. Med. Chem.*, 15 (7), 750–754 (1972).

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Paul H. Ginsburg

[57] **ABSTRACT**

11-(4-Piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines and their 5,6-dihydro derivatives are disclosed. The compounds are useful as antihistamines with little or no sedative effects.

13 Claims, No Drawings

EXHIBIT III

SCHERING CORPORATION

60 ORANGE STREET BLOOMFIELD, N. J. 07003

TELEPHONE: (201)429-4000
TELEX: 138163
CABLES: SCHERING BLOOMFIELD, N.J.

November 30, 1982

James P. Mann, M.D., Director
Division of Surgical-Dental Drug Products
National Center of Drugs and Biologics
HFD 160, Room 18B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: IND -- Sch-29851 Oral

Dear Doctor Mann:

Submitted herewith, in triplicate, is a "Notice of Claimed Investigational Exemption for a New Drug" for Sch-29851 Oral Capsules 20 and 40 mg., a non-sedating antihistamine.

Doctor Peter Galicky is the project physician for the subject IND.

Sincerely,

Nelson H. Schimmel, M.D.
Vice President
Regulatory Affairs

lk:hmd

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

EXHIBIT IV

Food and Drug Administration
Rockville MD 20857

January 6, 1983

IND 21,249

1 1983

Nelson H. Schimmel, M.D.

Schering Corporation
Attention: Nelson H. Schimmel, M.D.
60 Orange Street
Bloomfield, NJ 07003

Dear Dr. Schimmel:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 21,249

Sponsor: Schering Corporation

Name of Drug: Sch-29851 Capsules 20 & 40 mg.

Date of Submission: November 30, 1982

Date of Receipt: December 7, 1982

As sponsor of the clinical study proposed in this IND you are now free to obtain supplies of the investigational drug, but it is understood that studies in humans will not be initiated until 30 days after the date of receipt shown above. If, within the 30 day period, we notify you of serious deficiencies which require correction before human studies can begin or which require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

1 1987

Nelson A. Schimmel, M.D.

Please forward all future communications concerning this IND in triplicate, identified with this IND number, and addressed as follows:

National Center for Drugs and Biologics HFN 160
Attention: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

James P. Mann, M.D.
Director
Division of Surgical-Dental
Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

EXHIBIT V

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (201) 558-4000

October 31, 1986

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

SUBJECT: NDA 19-658 TRADEMARK (brand of loratadine) TABLETS 10 mg

Dear Dr. Russell:

Schering Corporation is submitting the New Drug Application for TRADEMARK (brand of loratadine) Tablets, 10 mg, in accordance with 21 CFR 314.50. TRADEMARK (brand of loratadine) TABLETS is a non-sedating antihistamine for the treatment of seasonal allergic rhinitis symptoms including nasal symptoms such as, sneezing rhinorrhea, stuffiness, pruritus, and ocular symptoms such as redness and itching; recommended dosing is 10 mg OD. The term Sch 29851 is the Schering designation for loratadine and is used extensively throughout the submission.

Although there were a number of studies conducted in support of this NDA including seasonal allergic rhinitis, wheal and flare, long-term safety, and special studies to demonstrate the lack of sedation, there are four studies which we believe clearly demonstrate the efficacy and safety of loratadine in the treatment of seasonal allergic rhinitis. They are the following:

	Volume
C84-008 Loratadine 10, 20, 40 mg OD vs Placebo	41
C84-111, C85-027 Loratadine 10 mg OD vs Clemastine 1 mg BID vs Placebo	41
I84-317 Loratadine 10 mg OD vs Terfenadine 60 mg BID vs Placebo	42

In reviewing this application, please refer to the following meetings which were held with the Surgical/Dental Division:

August 12, 1985 - End of Phase II Conference; discussion of clinical plans

July 10, 1986 - Pre-NDA Meeting; discussion of formatting the NDA

August 19, 1986 - Pre-NDA Meeting; discussion of content for Manufacturing/Controls section of the NDA

This application, which consists of 126 volumes, has been prepared according to the new format as described in Section 314.50 of the new NDA regulations, and in conformance with the draft guidelines as discussed at the Pre-NDA meetings. Specifically, with regard to the July 10, 1986 Pre-NDA clinical format meeting, we wish to confirm the following agreements:

Tachyphylaxis - This issue has been addressed. At your request, we have compared the number of dropouts on loratadine vs comparative agents and the timing of the dropouts.

Study Reports - Seven of the seasonal allergic rhinitis clinical study reports have been written according to the draft guidelines for the Clinical Data Section of the NDA. As agreed to at the End of Phase II Conference, since the remaining study reports were written prior to issuance of the guidelines, they were prepared using a slightly different format.

Patient Listings - Individual patient listings of demographics and symptom score data have been attached to each study report in compliance with the new guidelines.

Data Listings - A tabular display of the data from the case report forms is included in the Tabulations section, by parameter and by patient.

Case Reports - Case report forms included in this submission are only from patients who discontinued treatment due to adverse experiences. No deaths were reported during the studies.

Integrated Safety Summary - This summary includes a number of data presentations of treatment-related adverse reactions as well as clinical lab data.

Adverse Reactions

- The incidence of adverse reactions is presented in a number of tabular displays (e.g. body system, severe adverse experiences, patient dropouts due to adverse experiences).

- Adverse reactions from ongoing studies are not addressed in the above tables, but are discussed in the summary text. Further, it was agreed not to include patients in ongoing studies in the common denominator of patients treated with loratadine.

Laboratory Data

- Laboratory data has been presented in two tables. One table shows changes from baseline to the last value, or worst value in the case of long term safety studies, and include the mean percent change from baseline. Another table presents clinically significant changes in the lab values from baseline to last visit.

Finally, we wish to advise you that all the preclinical pharmacology, drug metabolism and toxicology reports previously submitted to the IND (#21,249) for loratadine have been reproduced in this application. The following preclinical reports were not been submitted to the IND, but are included in this NDA submission:

P-5111 Eighteen Month Oncology Study of Sch 29851 in Mice

P-5114 Twelve Month Oral Toxicity Study of Sch 29851 in Rats.

P-5155 Two-Year Oncogenicity Study of Sch 29851 in Rats.

P-5160 Comparative Distribution and Metabolism of Orall Administered ^{14}C-Loratadine in the Mouse and Rat.

P-5162 Identification of Loratadine Metabolites Isolated from the Urine of Humans, Monkeys and Rats.

The patent information, as required, is attached to the application form (Item 13). Additionally, samples are available pursuant to Item 10.a of the application form. These samples will be provided upon your request.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material are hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

We look forward to approval of this NDA.

Sincerely,

Alexander R. Giaquinto, Ph.D.
Vice President
Regulatory Affairs

TT:am

EXHIBIT VI

LAW DEPARTMENT
RECEIVED
NOV 12 '86

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

A. R. GIACOBBE

Food and Drug Administration
Rockville MD 20857

13

ROUTE TO
COMMENTS

NDA 19-658

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

5

Gentlemen:

We have received your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Loratadine Tablets 10 mg.

Date of Application: October 31, 1986

Date of Receipt: October 31, 1986

Our Reference Number: 19-658

Unless we find the application not acceptable for filing, the filing date will be December 31, 1986.

We will communicate with you further after we have had the opportunity to study the application. Please identify any communications concerning this application with the NDA number above. Should you have any questions concerning this NDA, please contact:

Conrad J. Ledet
Consumer Safety Officer
301-443-3500

All future communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics HFN-160
Attention: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Philip G. Walton, M.D.

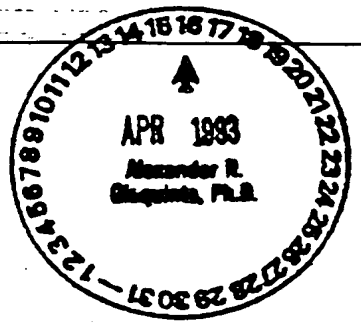
Patricia H. Russell, M.D.
Director
Division of Surgical-Dental
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

DEPARTMENT OF HEALTH & HUMAN SERVICES
EXHIBIT VII

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 1 2 1993



NDA 19-658

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Alexander R. Giaquinto, Ph.D.
Vice President, Worldwide Regulatory Affairs

Dear Dr. Giaquinto:

Please refer to your new drug application dated October 31, 1986, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Claritin (loratadine) Tablets, 10 mg.

We also refer to your amendments dated November 10, December 8 and 23, 1986, February 27, March 4 and 11, April 7, May 15, June 10 and 30, July 6 and 27, August 17, October 15, November 5, December 11 and 17, 1987, January 25 and 28, February 1, March 7, June 6, August 16, October 26, November 2, 23 and 30, December 22, 1988, April 24, May 18, June 20, July 18 and 26, August 1 and 3, September 6 (2) and 13, November 8, December 5 and 22, 1989, June 19, August 27, September 10, October 3 and 18, 1990, May 28, July 26, August 21 and 29, September 13 and 19, October 4, 16 (2), 22, 25 and 30, November 4 and 18, December 2, 9, 11, 18, 20 and 23, 1991, January 3, March 18, April 8, July 1, August 20 and 26, September 11, October 7, 9 and 20, November 18, 25 and 30, and December 11, 1992, January 15, March 22 and April 2, 1993.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis as recommended in the draft labels submitted October 16, 1991, the modified draft blister backing submitted October 20, 1992, and the draft package insert submitted April 2, 1993.

Accordingly, the application is approved, effective as of the date of this letter.

Marketing the product with labeling that is not identical to the draft labeling which is the subject of this letter may render the product misbranded and an unapproved new drug.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 19-658". Approval of the submission by FDA is not required before the labeling may be used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

We note the following post-approval commitments as stated in your November 18, 1992 and April 2, 1993 amendments:

1. To further study the efficacy of loratadine at lower doses;

2. to conduct interaction studies with erythromycin, ketoconazole and cimetidine;

3. to initiate development of a more sensitive analytical method for the detection of impurities;

4. to identify the specific enzyme systems responsible for the metabolism of loratadine; and,

5. to conduct studies to evaluate the pharmacokinetics and pharmacodynamics of loratadine based on sex and race.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT

EXHIBIT VIII

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,282,233
DATED : August 4, 1981
INVENTOR(S) : Frank J. Villani

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

ON THE TITLE PAGE:

Change inventor's name from "Frank J. Vilani" to

-- Frank J. Villani --.

Signed and Sealed this

Twenty-fourth Day of *November 1981*

Attest: Ruth M. Wrouf

Attesting Officer

GERALD J. MOSSINGHOFF

Commissioner of Patents and Trademarks

EXHIBIT IX

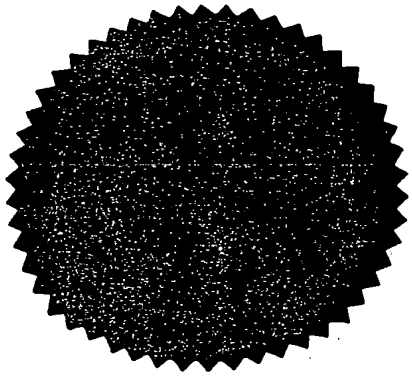
UNITED STATES PATENT AND TRADEMARK OFFICE

Certificate

Patent Number: 4,282,233 Patented: August 4, 1981

On petition requesting issuance of a certificate of correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above-identified patent, through error and without any deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is:
Frank J. Villani and Charles V. Magatti.

Signed and Sealed This Twenty-Sixth Day of December, 1989



Mary Lee
Supervisory Patent Examiner
Patent Examing Group 120
Art Unit 121
Organic Chemistry

EXHIBIT XI

Patent Case No. 2206

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent for:	
ANTIHISTAMINIC 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2-B]PYRIDINES	
Inventors: Frank J. Villani and Charles V. Magatti	
Patent No.: 4,282,233	
Issue Date: August 4, 1981	

Madison, New Jersey
November 5, 1990

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

REQUEST FOR RECORDING OF ASSIGNMENT
UNDER 37 C.F.R. 1.331

Please record the accompanying deed of assignment for the above identified patent on the Assignment Record of the United States Patent and Trademark Office.

Please return the recorded assignment to:

Stephen I. Miller
Schering-Plough Corporation
Patent Department
One Giralda Farms
Madison, New Jersey 07940-1000

Charge the $8.00 fee for recording this assignment and any other fee incident with this assignment to Deposit Account No. 19-0365. Triplicate copies of this document are enclosed for this purpose.

Respectfully submitted:

Stephen I. Miller
Registration No. 27927

ASSIGNMENT

For good and valuable consideration paid to me, Charles V. Magatti

of 63 Cumberland Avenue, Verona, New Jersey 07044

by SCHERING CORPORATION, a corporation organized under the laws of the State of New Jersey, United States of America, having its principal office at Galloping Hill Road, Kenilworth, New Jersey 07033, United States of America (hereinafter called "SCHERING"), I do hereby sell, assign and set over unto said SCHERING the entire right, title and interest in all countries of the world in and to any and all of my inventions and discoveries in ANTIHISTAMINE 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2-B]-PYRIDINES as described and/or claimed in United States Patent 4,282,233 which issued from United States Patent Application Serial Number 160,795, filed on June 19, 1980 and to any and all Letters Patent and applications granted and/or pending in any country of the world which derive their priority rights from said application 160,795 under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement to which the United States now is or hereafter becomes a signatory, and in and to any reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said SCHERING, its successors, assigns and other legal representatives, to the full ends of the terms for which a Letters Patent therefor may be granted, as fully and entirely as the same would have been held and enjoyed by me if this assignment and sale had not been made.

And I hereby covenant and agree that I will at any time, upon the request and at the expense of SCHERING, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, and Letters Patent and reissues, renewals and extensions thereof in SCHERING, its successors, assigns or other legal representatives, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and that I will, at any time, upon the request and the expense of SCHERING, execute any additional or divisional applications for patents for said inventions and discoveries, or any part or parts thereof, and applications for patents of confirmation, registration and importation based on said Letters Patent and on Letters Patent issuing from said additional or divisional applications and reissues, renewals and extensions therefor, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of SCHERING, its successors, assigns or other legal representatives.

Executed this 31 day of October, 19 90.

Charles V. Magatti L.S.

Charles V. Magatti

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Essex)

On this 31st day of October 19 90,
personally appeared before me Charles V. Magatti
to me known, and known by me to be the same described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

JoAnn O'Dell
Notary Public

JoANN O'DELL
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES JAN. 12, 1993

EXHIBIT XII

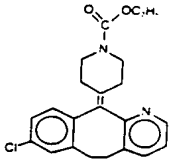
R 1 2 5 7 1 2

F-17544527 0102

CLARITIN®
brand of loratadine
TABLETS
Long-Acting Antihistamine

DESCRIPTION CLARITIN Tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. They also contain the following inactive ingredients: corn starch, lactose, and magnesium stearate.

Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$; its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate and has the following structural formula:



CLINICAL PHARMACOLOGY Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated 10 mg oral doses of CLARITIN Tablets have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with CLARITIN Tablets.

Pharmacokinetic studies following single and multiple oral doses of loratadine in 115 volunteers showed that CLARITIN Tablets are rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxyloratadine). The specific enzyme systems responsible for metabolism have not been identified. Approximately 80% of the total dose administered can be found equally distributed between urine and feces in the form of metabolic products after 10 days. The mean elimination half-lives found in studies in normal adult subjects (n = 54) were 8.4 hours (range = 3 to 20 hours) for CLARITIN Tablets and 28 hours (range = 8.8 to 92 hours) for the major active metabolite (descarboethoxyloratadine). In nearly all patients, exposure (AUC) to the metabolite is greater than exposure to parent loratadine.

In a study involving twelve healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (Cmax) of both CLARITIN Tablets and descarboethoxyloratadine were significantly higher (approximately 50% increased) than in studies of younger subjects. The mean elimination half-lives for the elderly subjects were 18.2 hours (range = 6.7 to 37 hours) for CLARITIN Tablets and 17.5 hours (range = 11 to 38 hours) for the active metabolite.

CLARITIN Tablets, dosed once daily, had reached steady-state by the fifth daily dose. The pharmacokinetics of CLARITIN Tablets and descarboethoxyloratadine are dose independent over the dose range of 10 to 40 mg and are not significantly altered by the duration of treatment.

In the clinical efficacy studies, CLARITIN Tablets were administered before meals. In a single-dose study, food increased the AUC of CLARITIN Tablets by approximately 40% and of descarboethoxyloratadine by approximately 15%. The time to peak plasma concentration (Tmax) of CLARITIN Tablets and descarboethoxyloratadine was delayed by 1 hour with a meal. Although these differences would not be expected to be clinically important, CLARITIN Tablets should be administered on an empty stomach.

In patients with chronic renal impairment (Creatinine Clearance ≤ 30 mL/min) both the AUC and peak plasma levels (Cmax) increased on average by approximately 73% for CLARITIN Tablets; and approximately by 120% for descarboethoxyloratadine, compared to individuals with normal renal function. The mean elimination half-lives of CLARITIN Tablets (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not significantly different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of CLARITIN Tablets or its active metabolite (descarboethoxyloratadine) in subjects with chronic renal impairment.

In patients with chronic alcoholic liver disease the AUC and peak plasma levels (Cmax) of CLARITIN Tablets were double while the pharmacokinetic profile of the active metabolite (descarboethoxyloratadine) was not significantly changed from that in normals. The elimination half-lives for CLARITIN Tablets and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

There was considerable variability in the pharmacokinetic data in all studies of CLARITIN Tablets, probably due to the extensive first-pass metabolism. Individual histograms of area under the curve, clearance, and volume of distribution showed a log normal distribution with a 25-fold range in distribution in healthy subjects.

CLARITIN Tablets are about 97% bound to plasma proteins at the expected concentrations (2.5 to 100 ng/mL) after a therapeutic dose. CLARITIN Tablets do not affect the plasma protein binding of warfarin and digoxin. The metabolite descarboethoxyloratadine is 73% to 77% bound to plasma proteins (at 0.5 to 100 ng/mL).

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

Clinical trials of CLARITIN Tablets involved over 10,700 patients who received either CLARITIN Tablets or another antihistamine and/or placebo in double-blind randomized controlled studies. In placebo-controlled trials, 10 mg once daily of CLARITIN Tablets was superior to placebo and similar to clemastine (1 mg BID) or terfenadine (60 mg BID) in effects on nasal and non-nasal symptoms of allergic rhinitis. In these studies, somnolence occurred less frequently with CLARITIN Tablets than with clemastine and at about the same frequency as terfenadine or placebo. In studies with CLARITIN Tablets at doses 2 to 4 times higher than the recommended dose of 10 mg, a dose-related increase in the incidence of somnolence was observed. Therefore, some patients, particularly those with hepatic or renal impairment and the elderly, may experience somnolence.

In a study in which CLARITIN Tablets were administered at 4 times the clinical dose for 90 days, no clinically significant increase in the QTc was seen on ECGs.

INDICATIONS AND USAGE CLARITIN Tablets are indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis.

CONTRAINDICATIONS CLARITIN Tablets are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

PRECAUTIONS **General:** Patients with liver impairment should be given a lower initial dose (10 mg every other day) because they have reduced clearance of CLARITIN Tablets.

Drug Interactions: Drugs known to inhibit hepatic metabolism should be coadministered with caution until definitive interaction studies can be completed. The number of subjects who concomitantly received macrolide antibiotics, ketoconazole, cimetidine, ranitidine, or theophylline along with CLARITIN Tablets in controlled clinical trials is too small to rule out possible drug-drug interactions. There does not appear to be an increase in adverse events in subjects who received oral contraceptives and CLARITIN Tablets compared to placebo.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In an 18-month oncogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (active metabolite) times higher than a human given 10 mg/day. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (active metabolite) times higher than a human given 10 mg/day. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of CLARITIN Tablets is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (AMES) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (Rat Primary Hepatocyte Unscheduled DNA Assay) or in two assays for chromosomal aberrations (Human Peripheral Blood Lymphocyte Clastogenesis Assay and the Mouse Bone Marrow Erythrocyte Micronucleus Assay). In the Mouse Lymphoma Assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Loratadine administration produced hepatic microsomal enzyme induction in the mouse at 40 mg/kg and rat at 25 mg/kg, but not at lower doses.

Decreased fertility in male rats, shown by lower female conception rates, occurred at approximately 64 mg/kg and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at doses of approximately 24 mg/kg.

Pregnancy Category B: There was no evidence of animal teratogenicity in studies performed in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CLARITIN Tablets should be used during pregnancy only if clearly needed.

Nursing Mothers: Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for the parent and active metabolite, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and metabolite was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS Approximately 90,000 patients received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day varied from 2 weeks' to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2% in both the treated and placebo groups.

REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF MORE THAN 2% IN PLACEBO-CONTROLLED ALLERGIC RHINITIS CLINICAL TRIALS

PERCENT OF PATIENTS REPORTING

	LORATADINE 10 mg QD n = 1926	PLACEBO n = 2545	CLEMASTINE 1 mg BID n = 536	TERFENADINE 60 mg BID n = 684
Headache	12	11	8	8
Somnolence	8	6	22	9
Fatigue	4	3	10	2
Dry Mouth	3	2	4	3

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of non-white subjects was relatively small.

In addition to those adverse events reported above, the following adverse events have been reported in 2% or fewer patients.

Autonomic Nervous System Altered salivation, increased sweating, altered lacrimation, hypoesthesia, impotence, thirst, flushing.

Body As A Whole Conjunctivitis, blurred vision, earache, eye pain, tinnitus, asthenia, weight gain, back pain, leg cramps, malaise, chest pain, rigors, fever, aggravated allergy, upper respiratory infection, angioneurotic edema.

Cardiovascular System Hypotension, hypertension, palpitations, syncope, tachycardia.

Central and Peripheral Nervous System Hyperkinesia, blepharospasm, paresthesia, dizziness, migraine, tremor, vertigo, dysphonia.

Gastrointestinal System Abdominal distress, nausea, vomiting, flatulence, gastritis, constipation, diarrhea, altered taste, increased appetite, anorexia, dyspepsia, stomatitis, toothache.

Musculoskeletal System Arthralgia, myalgia.

Psychiatric Anxiety, depression, agitation, insomnia, paronirla, amnesia, impaired concentration, confusion, decreased libido, nervousness.

Reproductive System Breast pain, menorrhagia, dysmenorrhea, vaginitis.

Respiratory System Nasal dryness, epistaxis, pharyngitis, dyspnea, nasal congestion, coughing, rhinitis, hemoptysis, sinusitis, sneezing, bronchospasm, bronchitis, laryngitis.

Skin and Appendages Dermatitis, dry hair, dry skin, urticaria, rash, pruritus, photosensitivity reaction, purpura.

Urinary System Urinary discoloration, altered micturition.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: peripheral edema; abnormal hepatic function including jaundice, hepatitis, and hepatic necrosis; alopecia; seizures; breast enlargement; erythema multiforme.

DRUG ABUSE AND DEPENDENCE There is no information to indicate that abuse or dependency occurs with CLARITIN Tablets.

OVERDOSAGE Somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg (40 to 180 mg). In the event of overdosage, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdosage would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

Oral LD_{50} values for loratadine were greater than 5000 mg/kg in rats and mice. Doses as high as 10 times the recommended clinical doses showed no effects in rats, mice, and monkeys.

DOSAGE AND ADMINISTRATION Adults and children 12 years of age and over: One 10 mg tablet daily on an empty stomach.

In patients with liver failure, 10 mg every other day should be the starting dose.

HOW SUPPLIED CLARITIN Tablets, 10 mg, white to off-white compressed tablets; impressed with the product identification number "458" on one side; and "CLARITIN 10" on the other; high density polyethylene plastic bottles of 100 (NDC 0085-0458-03). Also available, CLARITIN Unit-of-Use packages of 14 tablets (7 tablets per blister card) (NDC 0085-0458-01) and 30 tablets (10 tablets per blister card) (NDC 0085-0458-05); and 10 x 10 tablet Unit Dose-Hospital Pack (NDC 0085-0458-04)

Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from excessive moisture. Store between 2° and 30°C (36° and 86°F).

CLARITIN®
brand of loratadine
TABLETS
Long-Acting Antihistamine

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 4-93

B-17544527

EXHIBIT XIII

Brief Description of Significant Activities During Regulatory Review Period for CLARITIN® (brand of Loratadine SCH 29851) Tablets

Document Date*	Comment
11/30/82	Original IND Submission.
1/6/83	FDA Acknowledgement Letter (IND number 21,249 assigned).
1/7/83	Internal memo summarizing 1/5/83 telephone conversations with FDA; IND received 12/7/82, IND number 21,249 assigned; permission to proceed with study if limited dosing is followed.
1/7/83	Internal memo summarizing telephone conversations with FDA 1/5/83 and 1/6/83 regarding maximum dosing; FDA withdrew objections to it with recommendation that we do not undertake multiple dosing until further toxicology studies support it; informed him we were planning to initiate one. FDA also requested pharmacokinetic studies in man which we plan to undertake.
1/10/83	Agreement reached concerning initial rising single-dose safety and tolerance study and subsequent Phase I clinical studies between Schering and FDA.
1/17/83	FDA Acknowledgement letter (IND number assigned).
2/16/83	Curriculum vitae ("CV") for study monitor of study No. C82-104-01. As requested by FDA in 2/15/83 telephone conversation.
2/25/83	FDA letter requesting comparative pharmacokinetic data lab animals and human; comments on manufacturing and controls and stability portion. Response requested in 60 days.
4/26/83	Our response to the 2/25/83 FDA letter.
6/9/83	New protocol and investigator; technical amendment to Attachments 2, 3, 5.
9/23/83	New protocol and investigator; technical amendment to Attachments 2, 3, 5.
10/5/83	New protocol and investigator; technical amendment to Attachments 2, 3, 4, 5.
10/6/83	New protocol and investigator.
12/2/83	Updated technical information promised in our 10/5/83 letter to the FDA.
1/10/84	New protocol and investigator; technical amendment to Attachments 3, 4, 5. Completion of toxicity study on lab animals and humans requested in the 2/25/83 FDA letter to be reported in Annual Progress Report.

Document Date*	Comment
1/26/84	Annual Progress Report promised in our 1/10/84 letter submitted.
2/22/84	Biopharmaceutics Division of FDA comments on our 10/5/83 submission regarding tritiated compounds.
2/24/84	New Protocol and name and CV of new investigation submitted.
4/26/84	New protocol and five investigators; technical amendment to Attachments 3, 5; new project physician.
4/26/84	New protocol and five investigators.
4/26/84	New protocol and four investigators.
5/4/86	Updated Investigator's Brochure submitted.
8/1/84	New protocol and four investigators; technical amendment to Attachments 2, 3, 4, 5.
8/7/84	Seven new investigators to protocol submitted 8/1/84.
8/9/84	Three new investigators to protocol submitted 8/1/84.
9/13/84	Letter from FDA recommending future clinical trials for protocol submitted 8/1/84 be or longer duration for determination of tachyphylaxis and long term safety.
10/3/84	Adverse drug reaction ("ADR") to international study (I84-205-01); not conducted under our IND.
10/15/84	Follow-up to ADR submitted on 10/3/84.
10/25/84	New protocol and investigator; technical amendment to Attachments 2, 3, 4 and 5.
11/8/84	New protocol and investigator; new project physician for subject IND.
11/28/84	New protocol and investigator; technical amendment to Attachments 2, 3, 5.
11/29/84	Submission of case report forms promised in our 11/8/84 and 11/28/84 letters to FDA.
12/3/84	New protocol and investigator.
1/18/85	Amendment to our 4/26/84 protocol.
2/8/85	Updated Investigators Brochure; technical amendment to Attachment 5 (revised drug substance specifications and procedures).
2/11/85	Annual Progress Report; Attachment 5 (updated stability) and Attachment 6 (preclinical reports).
3/12/85	Request to FDA for End of Phase II Conference and to discuss our plans for Phase III

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	program; clinical, drug metabolism and toxicology information provided for the Conference.
3/15/85	New protocol and new investigator.
3/15/85	New protocol and new investigator.
3/25/85	New protocol and new investigator.
3/29/85	Internal memo summarizing 3/26/85 telephone conversation with FDA regarding summary of information submitted 3/12/85 for proposed End of Phase II Conference. FDA requests inclusion of manufacturing and controls overview at meeting; also, discussed what clinical/ biopharmaceutical/preclinical data should be included. Will establish meeting date in 4-6 weeks.
4/1/85	New investigator added to protocol submitted 3/25/85.
4/2/85	Two new investigators added to protocols submitted 3/25/85 and 4/1/85.
4/16/85	New protocol and investigator.
4/24/85	New investigator added to protocols submitted 3/25/85, 4/1/85 and 4/2/85.
4/24/85	FDA letter recommending extension of treatment duration for a study protocol submitted 3/2/85.
5/7/85	Internal memo summarizing 4/25/85 telephone conversation with FDA regarding a "hold" on a clinical study we are conducting pending further FDA discussion. FDA called back and agreed clinical study could continue. We agreed to send information regarding completed reports on rat and monkey studies; also, clinical study and protocol.
5/7/85	Submitted completed toxicology studies to summaries submitted 3/12/85; also, copy of protocol requested by FDA in 4/25/85 telephone conversation.
5/9/85	Responsive to 3/21/85 and 3/26/85 FDA telephone requests, we provided additional information to supplement our 3/12/85 submission for End of Phase II Conference; Pharmacology/Toxicology/Drug Metabolism/Clinical/Manufacturing and Controls were included.
5/10/85	Revision to protocol submitted 3/15/85.
5/16/85	FDA letter discussing pharmacology review of rat study; also, comments about continuation of study; agreed to continuation. Request for case report forms and a revision of our 3/15/85 protocol for Dr. Herron regarding exclusion criteria.

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5/20/85	New investigator for protocols submitted 3/25/85, 4/1/85, 4/2/85 and 4/25/85.
5/20/85	Submission of information requested by FDA in its 5/16/85 letter and in the 4/25/85 and 4/26/85 telephone conversations; clinical study report and Schering's policy on exclusion criteria submitted.
6/13/85	New investigator to protocol submitted 3/15/85.
6/14/85	New protocol and investigator.
6/17/85	New protocol and investigator.
6/19/85	Confirmation of End of Phase II Conference for 8/12/85; four copies of 5/9/85 submission sent.
6/20/85	Responsive to 4/24/85 FDA letter, Schering made a decision to stay with two-week treatment and not extend treatment duration.
7/2/85	FDA letter providing Division of Biometrics comments on protocol submitted 8/1/84; response requested within 60 days.
7/18/85	FDA letter referring to our 6/20/85 submission and repeating FDA position stated in its 4/24/85 letter for an extension of treatment duration.
8/7/85	Letter informing FDA we will discuss FDA 7/18/85 recommendation at the End of Phase II Conference scheduled for 8/12/85.
8/7/85	Our responses to comments made in FDA letter dated 7/2/85.
8/14/85	New protocol and investigator; technical amendment to Attachments 2, 5.
8/21/85	New protocol and three investigators; technical amendment to Attachments 2, 3, 5.
8/27/85	New investigator to protocol submitted 8/21/85.
9/4/85	New investigator to protocol submitted 8/21/85.
9/9/85	Final segment III study report submitted, as discussed at End of Phase II Conference held 8/12/85.
9/10/85	New investigator to protocol submitted 8/21/85.
9/16/85	FDA letter providing Division of Biopharmaceutics comments on our 3/12/85 and 5/9/85 submissions; guidelines for specific and sensitive analytical assay methods suggested.
9/18/85	New protocol and investigator.

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10/2/85	Letter sent to FDA with our understanding of agreements reached at End of Phase II Conference of 8/12/85 regarding Toxicology/ Pharmacology/Drug Metabolism/ Statistics/ Clinical and Division of Biopharmaceutics comments of 9/16/85.
10/14/85	New protocol and investigator.
10/21/85	Three new investigators to protocol submitted 10/14/85.
11/4/85	New investigator to protocol submitted 10/14/85.
11/5/85	New investigator to protocol submitted 10/14/85.
11/8/85	New protocol and investigator; technical amendment to Attachments 2, 3, 5.
11/12/85	New protocol and investigator; technical amendment to Attachments 2, 3, 5.
11/12/85	Two new investigators to protocol submitted 11/18/85.
11/15/85	Two new investigators to protocol submitted 11/8/85.
11/19/85	New investigator to protocol submitted 11/8/85.
11/20/85	New investigator to protocol submitted 11/8/85.
11/21/85	New investigator to protocol submitted 11/8/85.
11/21/85	New investigator to protocol submitted 11/8/85.
11/22/85	New investigator to protocol submitted 11/8/85.
11/26//85	New investigator to protocol submitted 11/8/85.
12/5/85	Principal co-investigators to protocol submitted 11/8/85.
12/18/85	FDA letter dated 12/18/85 from Division of Biopharmaceutics advises us that analytical assay must be highly specific to each compound found in biological fluid in protocol submitted 9/5/85 and to extend Exclusion Criteria in protocols submitted 9/4/85, 10/14/85 and 11/8/85.
2/20/86	Internal memo summarizing conversation with FDA regarding OTC status for product.
2/28/86	Submitted Progress Report which included updated stability, preclinical, clinical data.

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3/3/86	Information sent to FDA as promised at End of Phase II Conference on 8/12/85 and in response to questions raised by Division of Biopharmaceutics in FDA letters of 9/16/85 and 12/18/85 regarding Drug Metabolism and Pharmacology.
3/31/86	Letter to FDA regarding adverse reaction report; no follow-up expected.
4/25/86	New protocol and investigator.
5/13/86	Technical amendment to IND: Attachments 4 and 5.
5/19/86 (N)	Request for Pre-NDA meeting to discuss format and data presentation under NDA new draft guidelines.
7/23/86	Amendment to include five preclinical study reports.
7/30/86 (N)	Confirmation of Technical Pre-NDA meeting set for 8/19/86 regarding manufacturing and controls data.
8/1/86 (N)	Advance manufacturing and controls data submitted to FDA for Technical Pre-NDA meeting of 8/19/86.
8/20/86 (N)	Internal memo summarizing Action Items discussed at Pre-NDA Technical meeting with FDA on 8/19/86.
8/26/86 (N)	Pre-NDA 7/10/86 Meeting Minutes: End of Phase II Conference agreements; scope of NDA clinical program and clinical data presentation/ format.
8/27/86	New protocol and five investigators.
8/28/86	New investigator to protocol submitted 8/27/86.
9/11/86	Letter confirming meeting scheduled for 9/25/86 to discuss alternatives to Rx and OTC switches via conventional methods concept.
9/16/86	New investigator to protocol submitted 8/27/86.
9/19/86 (N)	Internal memo summarizing Pre-NDA Technical meeting with FDA on 8/19/86 to review chemical synthesis, pharmaceutical development and analytical/ stability information in advance of NDA submission planned for 10/86.
9/26/86 (N)	Letter and copy of our notes on meeting with FDA held on 8/19/86, including our understanding or suggestions and agreements regarding technical information to be included in NDA.
10/15/86	Type II Drug Master File for loratadine submitted for manufacture of loratadine at

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	Irish Fine Chemicals, Rathdrum, County Wicklow, Ireland.
10/21/86	New protocol and investigator.
10/31/86 (N)	New Drug Application ("NDA") #19-658 submitted.
11/5/86 (N)	FDA acknowledgement letter of 11/5/86: NDA filing date of 12/31/86 will be assigned.
11/10/86 (N)	Duplicate copies of statistical reports submitted on 10/31/86 to NDA and copy of protocol study C83-076-01, which had been amended to IND (desk copy) submitted.
11/10/86 (N)	Amendment to NDA submitted 10/31/86 entitled "General Aspects of Study Design Used in Common" for several studies submitted on 10/31/86 but not been included in the original NDA was submitted.
11/18/86 (N)	Duplicate copies of documents sent on 10/31/86 to Medical Officer on Preclinical Pharmacology Drug Metabolism Reports regarding drug distribution across blood brain barriers.
12/8/86 (N)	Partition coefficient and pKa data of loratadine and variance tables for Study C84-111 submitted.
12/23/86 (N)	Information regarding high percent change in post therapy mean values for phosphorous and creatinine of patients in clinical trials submitted.
1/12/87	Annual progress report; stability, pre-clinical, clinical biographies and a clinical report submitted.
1/28/87 (N)	FDA letter of 1/28/87 regarding manufacturing and controls deficiencies; and request that response be sent as one complete submission.
1/29/87 (N)	Internal memo summarizing telephone conversation 1/28/87 with Biopharmaceutics Division regarding drug metabolite potency.
1/29/87 (N)	Internal memos summarizing 1/28/87 telephone discussion with FDA regarding RX to OTC switch program for loratadine. FDA unable to comment on it at this time.
2/3/87 (N)	CVs, protocols, Form 1572's and case report forms for first five (5) patients of five studies sent to Clinical Investigation Branch.
2/27/87 (N)	Four-month safety update for loratadine to NDA submitted 10/31/86.
3/4/87 (N)	Final toxicology report, a 17-month oral toxicity study submitted.

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3/11/87 (N)	Responsive to FDA telephone inquiry we submitted loratadine half-life data to support once-a-day drug administration.
3/16/87 (N)	Acknowledgement letter by FDA of receipt of our 3/4/87 submission; 60-day review clock extension.
3/30/87 (N)	Internal memo summarizing 3/26/87 telephone conversation with FDA pharmacologist who called 3/26/87 regarding pK_a values and partition coefficients for loratadine metabolite.
4/7/87 (N)	Responsive to FDA request, we submitted additional information regarding international studies included in original NDA submitted on 10/31/86.
4/16/87 (N)	Additional information on two adverse experiences reported in our 2/27/87 letter re four month post NDA safety update submission.
4/20/87 (N)	Internal memo summarizing 4/17/87 telephone conversation; FDA request for total percent Adverse Drug Reaction reports for all studies; they were informed where integrated summary could be found in NDA.
4/21/87	Technical amendment to Attachment 5 of IND to provide for child-resistant caps on packages used in clinical trials.
5/5/87 (N)	Internal memo summarizing 5/1/87 telephonic conference call with FDA regarding low CNS penetration of loratadine; pK_a values and partition coefficients for loratadine metabolite also discussed.
5/14/87 (N)	Adverse event reported.
5/15/87 (N)	Responsive to FDA request, we submitted a completed copy of a 12 month oral toxicity study of loratadine inadvertently omitted from original NDA submitted 10/31/86.
5/22/87 (N)	Acknowledgement letter of our 5/15/87 submission; 60-day review clock extension.
6/2/87	New protocol and investigator.
6/5/87 (D)	Updated information to DMF 6626 for loratadine.
6/10/87 (N)	Responses to questions in FDA 1/28/87 letter on loratadine manufacturing and controls deficiencies, and three copies of Methods Validation information were provided.
6/24/87 (N)	FDA letter dated 6/24/89 acknowledging receipt of our 6/10/87 submission; 60-day review clock extension.
6/30/87 (N)	As requested by C. Ledet of FDA, copy of article on effect of some antihistamines on

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	reproductive organs of male rat submitted to NDA.
7/6/87 (N)	Replacement page sent for Production Stability Protocol for that submitted 6/10/87.
7/9/87 (N)	Formal request to Dr. Walters of FDA for meeting with FDA to discuss progress and status of NDA. (Telephone discussions with C. Ledet on 6/30/87.)
7/22/87 (N)	FDA letter dated 7/22/87 inviting us to a Pulmonary-Allergy Drug Advisory Committee meeting on October 22-23, 1987. Schering invited to make brief presentation on loratadine during closed session.
7/27/87 (N)	Per FDA requests a second copy of 7/6/87 submission sent to Dr. Patel of FDA who was unable to locate original copy.
8/6/87 (N)	FDA letter for Dr. Walters dated 8/6/87 providing Division of Biometrics comments on efficacy data submitted in original NDA submitted 10/31/86. Prompt response requested in order to continue review.
8/17/87	FDA letter dated 8/17/87 providing Division of Biometrics comments on animal pharmacology data. Additional data requested, particularly regarding tumor type.
8/17/87 (N)	Responses to Dr. Walters FDA 8/6/87 letter.
8/21/87 (N)	Internal memo summarizing 8/21/87 meeting with FDA to obtain directions regarding Pulmonary-Allergy Advisory Committee meeting, in which Schering has been invited to make a brief presentation on loratadine. Several points regarding Biometrics review letter of 8/6/87 also discussed.
8/25/87 (N)	As promised in a 8/24/87 telephone conversation, data summary of partition coefficients and pKa values of loratadine and its metabolite submitted.
8/26/87 (N)	Desk copy sent to Biometrics Division as discussed in the 8/21/87 FDA meeting and 8/26/87 telephone call.
9/1/87	New protocol and investigator.
9/3/87	New protocol and investigator.
9/4/87	New protocol and investigator; technical amendment to Attachments 2, 3, 5.
9/11/87 (N)	Internal memo summarizing telephonic discussions with FDA during week of 9/7/87 regarding our presentation to the Pulmonary-Allergy Advisory Committee on October 22-23, 1987.
9/22/87 (N)	Internal memo summarizing telephonic conversations on 9/21/87 and 9/22/87;

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	statistical review discussed. Presentation will not be made at Pulmonary-Allergy Advisory Meeting; only summary of polled somulence and psychiatric disorder data.
9/22/87 (N)	Internal memo summarizing telephone conversation 9/21/87 with Biometrics Division. Discussion of statistical data and analysis of efficacy dose response.
9/23/87 (N)	Advance summaries of loratadine presentation submitted to Pulmonary-Allergy Advisory Committee for October 22-23, 1987 meeting.
9/28/87	Information Amendment: Nonclinical Pharmacology and Toxicology reports submitted.
10/1/87	New investigator to protocol submitted 9/3/87.
10/1/87	New investigator to protocol submitted 9/3/87.
10/7/87	FDA letter dated 10/7/87: comments on protocol submitted 9/3/87 regarding use of Terfenadine dosage, primary outcome(s), time point(s) and participating center.
10/15/87	Clinical report submitted.
10/15/87 (N)	Clinical report. An Information Amendment entitled: The Effects of Loratadine Alone and in Combination with Alcohol on Actual Driving Performance submitted to NDA.
10/19/87 (N)	Internal memo summarizing 10/19/87 telephone conversation with FDA assuring them we would not present O'Hanlon report to Pulmonary-Allergy Advisory Committee meeting, October 22-23, 1987.
10/20/87 (N)	FDA Letter acknowledging our 10/15/87 submission; 90-day review clock extension.
10/21/87 (N)	Internal memo summarizing 10/20/87 telephonic request from FDA that we present data from O'Hanlon report to Pulmonary-Allergy Advisory Committee meeting October 22-23, 1987.
10/26/87 (N)	Hard copy of slide presentation for Pulmonary-Allergy Advisory Committee meeting held 10/23/87 regarding FDA's statistical questions (8/6/87 FDA letter; response by Schering 8/17/87).
10/27/87 (N)	Minutes of 9/21/87 meeting with FDA sent to them regarding statistical questions.
11/5/87 (N)	Report on retabulation of animal tumor data on loratadine (FDA request in 8/17/87 letter) and Additional Statistical Analysis of loratadine (FDA request at 9/21/87 meeting).
11/5/87 (N)	Internal memo summarizing 11/5/97 telephone conversation with FDA that Medical review completed and approvable. Pharmacology

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	review awaiting response to FDA 8/17/87 comments. O'Hanlon report submitted for Neuropharmacology review.
11/12/87 (N)	Letter to FDA confirming proposed meeting 1/88 to discuss moving loratadine from Rx to OTC status.
11/12/87 (N)	Internal memo summarizing telephone discussion with FDA regarding O'Hanlon report which was sent only for completeness of clinical obligation; and which will not used for labeling support. Also, discussed draft Summary Basis of Approval. Biopharmaceutical review outstanding.
11/13/87 (N)	Acknowledgement letter of our submission 11/5/87; 60-day review clock extension.
11/13/87 (N)	Letter to FDA regarding our 10/15/87 submission. We fulfilled our obligation under 21 CFR section 314.50 (d)(5)(iv) to report all clinical information, we do not consider it a major amendment and are not utilizing data to support label indications.
11/13/87	Two new investigators to protocol submitted 9/3/87.
11/13/87	New protocol and investigator.
11/23/87	FDA letter dated 11/23/87: comments regarding protocol submitted 10/21/86 comments Division of Biometrics. Response requested in 60 days.
12/1/87 (N)	Internal memo summarizing telephone conversation with FDA to inquire about status of NDA review. They do not have anything to discuss at the present time.
12/2/87 (N)	As requested by FDA, sent three copies of our draft summary basis of approval to NDA.
12/3/87 (N)	Internal memo summarizing numerous telephone conversations with FDA to inquire about status of loratadine NDA review.
12/7/87 (N)	Internal memo summarizing 12/7/87 telephonic discussions regarding sedating vs. nonsedating nature of antihistamines, e.g., terfenadine/loratadine and O'Hanlon report with Dr. Straus of FDA who requested that Neuropharmacology review of the report was needed. We feel full review unnecessary as we do not plan to use it in our labeling claims. We may seek another approach to this through other FDA personnel.
12/7/87 (N)	Internal memo summarizing 12/7/87 telephone discussions with Dr. Friedberg who requests additional retabulated carcinogenicity studies in mouse and rat requested by Biopharmaceutical Division.
12/10/87 (N)	Internal memo summarizing 12/10/87 telephone conversation with Acting Director of

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	Surgical-Dental Division that O'Hanlon study will not delay approval of loratadine.
12/11/87 (N)	Trademark for subject NDA (loratadine) has been assigned; trademark is CLARITIN™.
12/11/87 (N)	As requested by Dr. Friedberg of FDA on 12/7/87 telephone call, retabulation of carcinogenicity studies in mouse and rat submitted.
12/14/87 (N)	Internal memo summarizing 12/14/87 telephone conversation with FDA regarding additional retabulated carcinogenicity studies requested.
12/17/87 (N)	As requested in 12/14/87 FDA telephone conversation with Dr. Friedberg, additional retabulated carcinogenicity studies in mouse and rat submitted.
12/21/87 (N)	Internal memo summarizing 12/21/87 telephone conversation with FDA that they had received our letter identifying CLARITIN™ as our trademark for loratadine. FDA did not feel we needed to come down to discuss our labeling with them.
12/22/87 (N)	Internal memo summarizing 12/22/87 telephone conversation with FDA; they again felt it was not necessary to discuss our labeling with them.
12/29/87 (N)	FDA letter dated 12/29/87 with cursory review of drug names similar to our trademark CLARITIN™.
1/6/88	Internal memo summarizing 1/6/88 FDA telephone conversation; status of clinical study 87-089-01. We informed them study started and results would be submitted when completed.
1/6/88 (N)	Internal memo summarizing 1/6/88 telephone conversation; discussed status of biopharmaceutical review regarding product used in pivotal clinical efficacy/safety studies, dose-proportionality data. Agreed to call him back with responses.
1/8/88 (N)	Internal memo summarizing 1/7/88 telephone conversation. FDA would like to review our proposed packaging; we will send it to them on 1/11/88.
1/11/88 (N)	Proposed labeling for CLARITIN™ submitted.
1/12/88 (N)	Internal memo summarizing 1/12/88 telephone discussion with FDA regarding Biopharmaceutical review, particularly bioavailability and bioequivalency data.
1/14/88 (N)	Internal memo summarizing 1/14/88 telephone discussion with FDA regarding confidence limits and dose proportionality. Reminded

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	them of agreements in Pre-NDA meeting 7/10/86; will sent copy of minutes.
1/15/88 (N)	Response to FDA letter of 12/29/87 regarding similar trademarks; none of these are currently active in U.S. We plan to use CLARITIN™ as our trademark for loratadine.
1/15/88 (N)	Clarification of agreement (in a 12/10/87 telephone conversation) that approvability of NDA would not be delayed pending neuropharmacology review of study submitted 10/15/87.
1/19/88 (N)	Internal memo summarizing 1/19/88 telephone discussion regarding inconsistencies in last two carcinogenicity tumor data submissions.
1/20/88 (N)	Internal memo summarizing 1/20/88 telephone discussion with FDA regarding status of loratadine review, specifically Biopharmaceutic carcinogenicity tabulation.
1/20/88	Response to FDA 11/23/87 letter. Study completed. Questions relating to protocol will be submitted in final clinical report.
1/21/88 (N)	Internal memo summarizing 1/21/88 telephone discussion with FDA regarding retabulated carcinogenicity studies and 12/17/87 sent 11/5/87.
1/25/88	Responsive to a 1/12/88 telephone discussion with Dr. Hepp of FDA, we submitted amendment to NDA which included recalculation of bioequivalence data, pivotal clinical studies and Biopharmaceutics Section of Schering Pre-NDA Conference minutes 7/10/86.
1/28/88 (N)	Responsive to a 1/19/88 telephone conversation with Dr. Poochikian of FDA, additional response to Question 9 of FDA 1/28/87 letter. Four copies of Methods Validation Package, additional coding legend and data on unit dose packaging submitted.
2/1/88 (N)	FDA letter dated 2/1/88, acknowledges receipt of our letter of 1/25/88; 90-day review clock extension.
2/1/88 (N)	Letter of Dr. Walters of FDA, we sent a tabulation of historical tumor incidence data from rat and mouse species and explanation of differences in 8/17/87, 12/11/87 and 12/17/87 submissions.
2/3/88 (N)	Internal memo summarizing telephone discussion with FDA regarding retabulated carcinogenicity studies.
2/3/88 (N)	FDA letter acknowledging receipt of our 1/28/88 submission; 60-day review clock extension.

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2/4/88 (N)	Internal memo summarizing 2/4/88 telephone discussion with FDA regarding our bioequivalency submission of 1/25/88.
2/5/88 (N)	FDA letter dated 2/5/88 requesting samples be submitted to two FDA laboratories for method validation by 2/12/88.
2/12/88 (N)	As requested FDA in its 2/5/88 letter, samples submitted to FDA regional laboratory (Missouri).
2/12/88 (N)	As requested by FDA in its 2/5/88 letter samples submitted to FDA regional laboratory (New York).
2/16/88 (N)	Internal memo summarizing 2/16/88 telephone call from FDA inquiring if samples for Methods Validation had been sent to FDA regional laboratories; we informed them they had been sent 2/12/88.
2/18/88 (N)	Internal memo summarizing 2/18/88 telephone conversation; Biopharmaceutical and Biometrics reviews almost complete. Should be finished in two weeks.
2/22/88 (N)	Internal memo summarizing 2/22/88 call to FDA regarding Biometrics/Pharmacology review. Awaiting Biometrics review.
2/23/88 (N)	Internal memo summarizing our 2/23/88 call to FDA to assure them we would be sending blister packaging within ten days.
2/24/88	New protocol and CV of investigator sent to FDA.
3/7/88 (N)	Letter to Dr. Walters of FDA, Amendment to NDA by withdrawing foreign clinical studies M85-706A and I85-101 from consideration.
3/21/88 (N)	Letter to Dr. Walters of FDA enclosing minutes of a 2/8/88 meeting at the FDA whereat the loratadine drug substance was discussed.
4/27/88 (N)	Letter to Dr. Poochikian of FDA regarding blister cards of Claritin Tablets.
5/3/88	New protocol and two new investigators.
5/3/88	Internal memo summarizing 5/3/88 telephone conversation with FDA regarding impurities in loratadine.
5/16/88	New protocol and names of three new investigators submitted.
5/16/88 (N)	FDA letter dated 5/16/88 regarding comments by Division of Biometrics on our 4/7/87, 10/15/87 and 11/5/87 submissions.
5/17/88 (N)	Internal memo summarizing 5/17/88 telephone conversation with Dr. Poochikian (FDA review chemist) to ask what requirements would be needed to switch NDA for Tablet to Capsule.

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5/17/88	New protocol and names of two new investigators submitted.
5/19/88 (N)	Discussions with FDA regarding data base from study C85-06701.
5/23/88	Information Amendment: Chemistry/Microbiology sent to the FDA regarding protocol submitted on 5/17/88.
5/23/88 (N)	Reference is made to discussion with FDA on 5/19; Corrections and Recalculations of Sch 29851 Bioequivalence Data sent to FDA.
5/31/88	New protocol and CV of investigation sent to FDA.
6/5/88 (N)	Clinical study report C85-067-01 reissued "Bioavailability of Sch 29851 in Normal Male Volunteers".
6/6/88 (N)	Reference is made to recent discussions with Biopharmaceutic Division; Corrections and Recalculations of loratadine (Sch 29851) Bioequivalence Data Sent to Dr. Walters of FDA.
6/8/88	FDA letter commenting on our submission dated May 3, 1988; and requesting written response.
6/10/88 (N)	Letter to FDA submitting loratadine drug substance impurity data per 1/28/87 request by Dr. Russel of FDA.
6/10/88	FDA letter commenting on our submission dated May 17, 1988 of new protocols to be conducted by two new investigators and requesting written response.
6/14/88 (N)	Meeting with FDA to discuss use of loratadine in management of idiopathic chronic urticaria.
6/29/88 (N)	Internal memo summarizing 6/29/88 telephone conversation with FDA regarding loratadine drug substance impurities; FDA official recommended submitting requested information upon approval of NDA.
7/1/89 (N)	Letter to FDA summarizing 6/14/88 meeting.
7/6/88	Letter to FDA submitting three loratadine international study reports.
7/29/88	New protocol and CV of new investigation submitted.
8/8/88	Internal memo summarizing 8/8/88 meeting with FDA to outline potential strategy to convert loratadine Tablet NDA to loratadine Capsule NDA; FDA recommended submitting new Capsule NDA and cross-referenced to Tablet NDA and withdraw without prejudice current Tablet NDA.

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8/16/88 (N)	Loratadine Tablet/Capsule Bioequivalency, Study Synopsis C85-067 and Study report C88-053-01 submitted to Dr. Walters of FDA.
8/16/88	New protocol regarding loratadine Tablets vs Placebo in Seasonal Allergic Rhinitis and CV's of three new investigators and study sites submitted.
8/18/88	CV of additional investigation and study site for protocol sent 8/16/88 submitted to FDA.
8/22/88	CV of four new investigators and study site for protocol sent 8/10/88 submitted to the FDA.
8/23/88	CV of additional investigator and study site for protocol sent on 8/16/88 submitted to FDA.
8/23/88	Letter to FDA submitting internal memo summarizing 8/8/88 meeting and report of all available stability data for loratadine capsules.
8/29/88	Two additional investigators and study sites for protocol sent on 8/16/88 submitted to FDA.
9/12/88 (N)	Letter with proposed agenda for meeting with FDA regarding loratadine NDA.
9/15/88	New investigator and study site for protocol sent 8/16/88 submitted to the FDA.
9/20/88	FDA letter commenting on letters and amendments of July 29, 1988 and protocol submitted 8/10/88.
9/21/88	Internal memo summarizing telephone conversation with FDA regarding loratadine capsule stability.
10/12/88	Letter to FDA in response to 6/14/88 meeting; new protocol C88-067-10 "Multicenter Comparative Efficacy and Safety Study of Sch 29851 and Placebo in Management of Idiopathic Chronic Urticaria.
10/25/88 (N)	Letter and information sent in response to 10/5/88 FDA phone call.
10/26/88	Letter and information sent to FDA in response to the 6/8/88 FDA letter requesting loratadine Tablet information.
10/26/88	Letter and information sent to FDA in response to the 6/10/88 FDA letter requesting loratadine Tablet information.
10/26/88 (N)	Letter including slides and Minutes of FDA meeting of 10-21-88 regarding Tablet/Capsule bioequivalence sent per FDA request.
11/1/88	Letter to FDA responsive to FDA letter of 9/20/88 concerning proposed clinical studies C88-078-01 and C88-047.

Document Date*	Comment
11/1/88 (N)	FDA responsive to our NDA submitted 10/31/88 and acknowledging receipt of our amendment dated 10/26/88.
11/7/88 (N)	Letter to the FDA submitting Addendum to Study No. C85-067-01.
11/8/88	Letter to the FDA submitting chemistry, manufacturing and Control Data for Placebo Tablets for protocols submitted 7/29/88 and 8/10/88.
11/9/88 (N)	Internal memo summarizing 11/7/88 telephone conversation with FDA regarding study C85-060-01 Addendum to NDA telefaxed to FDA on 11/7/88.
11/10/88 (N)	Letter from FDA acknowledging receipt of our NDA dated 10/31/88 and an Amendment dated 11/7/88.
11/23/88 (N)	Clinical Study Synopsis C88-047 "Efficacy and Safety of loratadine Tablets vs Capsules vs Placebo in Patients with Seasonal Allergic Rhinitis" submitted to FDA.
11/30/88 (N)	Letter to FDA enclosing replacement page 24 for Clinical Study submitted 11/23/88.
11/23/88	Letter from FDA commenting upon our protocol C88-067-01 submitted 10/12/88.
11/30/88	FDA letter regarding our NDA submitted 10/31/88 and acknowledging receipt of our Amendment dated 11/23/88.
12/7/88 (N)	Internal memo summarizing telephone call from M. Friedberg (FDA) requesting retabulation of hepatocellular carcinoma and hepatocellular adenoma data.
12/16/88 (N)	Meeting with FDA regarding Study C88-047.
12/21/88	FDA letter commenting on our submissions dated 10/26/88 and 11/8/88.
12/22/88 (N)	Letter to Dr. Walters of FDA submitting data and material requested by FDA at 12/16/88 meeting.
1/9/89 (N)	Internal memo summarizing 1/6/89 telephone conversation with FDA regarding 12/10/88 meeting.
1/17/89	Internal memo summarizing 1/17/89 telephone call with FDA regarding 12/21/88 FDA letter.
1/31/89	Letter to FDA submitting annual report for loratadine Tablets.
2/21/89	FDA letter regarding our submissions dated 3/2 and 8/16/88.
3/1/89 (N)	Internal memo summarizing a 2/28/89 telephone conversation with FDA regarding loratadine pharmacokinetic data.

Document Date*	Comment
3/6/89	Letter to FDA submitting new protocol C88-067; and names of three new investigators who will conduct new study.
3/13/89 (N)	Letter to FDA regarding apparent variances in reported half-life of loratadine active metabolite.
3/15/89	Letter to FDA responsive to questions raised in FDA letter dated 11/23/88.
3/21/89 (N)	Internal memo summarizing 3/21/89 telephone conversation with FDA regarding new site to package loratadine Tablets.
3/28/89 (N)	FDA letter dated 3/28/889 regarding our 9/16/88 submission and commenting upon our study C88-053-01.
4/5/89	New protocol and names and CV's new investigator submitted.
4/12/89	New protocol and names and CV's new investigator submitted.
4/13/89	New protocol and names and CV's of two new investigators submitted.
4/19/89 (N)	Letter from FDA regarding our protocol C88-067 submitted 3/6/89.
4/24/89 (N)	Letter responsive to FDA letter of 3/28/89 regarding assay methodology and validation of plasma concentrations of loratadine and Sch 34117 (studies C85-067-01 and C88-053-01).
5/4/89	Letter to FDA submitting Clinical Study C86-049-01: "Comparative Study of the Acute and Chronic Effects on Skills Performance of loratadine (Sch 29851) BENEDRYL and Placebo alone and in Combination with Alcohol".
5/5/89 (N)	FDA letter regarding NDA submitted 10/31/86 and acknowledging receipt of our NDA amendment dated 4/24/89.
5/5/89 (N)	New protocol and name and CV of new investigator submitted.
5/9/89	Names and CV's of three new investigators for protocol previously submitted to FDA on 4/5/89.
5/10/89	Letter to FDA submitting material and data responsive to FDA letter dated 12/21/88.
5/11/89	Internal memo summarizing 5/11/89 telephone call with FDA.
5/18/89 (N)	Letter to FDA submitting material and data to amend our NDA submitted 10/31/86.
5/18/89	Letter to FDA submitting three preclinical reports on loratadine and the metabolite thereof and one drug metabolism report.

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5/18/89	Names and CV's of two new investigators for protocol submitted 5/5/89.
5/18/89	Letter to FDA summarizing a 5/5/89 telephone conversation regarding our 3/15/89 submission; and confirming FDA agreement to allow inclusion of women of child bearing agent in Study C88-067-01.
5/26/89	FDA letter providing comments and questions regarding our submission on 4/5/89 of protocol C89-002-02.
6/5/89 (N)	Internal memo summarizing a 6/5/89 telephone conversation with the FDA regarding loratadine NDA.
6/19/89	Name and CV of new investigator submitted for protocol submitted 5/5/89.
6/19/89	Name and CV of new investigator for protocol submitted 4/5/89.
6/20/89 (N)	Letter to FDA submitting information requested by FDA in a 6/19/89 telephone conversation with C. Ledet of FDA.
7/11/89	Name and CV of new investigator for protocol submitted on 5/5/89.
7/11/89	Letter to FDA resubmitting four volumes of information originally submitted to FDA on 4/24/89 in response to FDA letter of 3/28/89.
7/18/89 (N)	Letter to FDA submitting information from studies C84-11 and C85-027 requested by C. Ledet of FDA in a 7/10/89 telephone call.
7/26/89 (N)	Letter to Dr. Burke of FDA in response to 7/26/89 telephone call - resubmitting copies of volumes 1.56 to 1.62 of NDA originally submitted on 10/31/89.
7/26/89 (N)	Letter to Dr. Burke of FDA in response to a 7/21/89 telephone FDA request for safety update for loratadine Tablets.
8/1/89 (N)	Revised loratadine package insert submitted responsive to 7/21/89 telephone conversation with Dr. Straus (FDA).
8/3/89 (N)	Letter to FDA submitting document to replace one submitted on 8/1/89.
8/4/89 (N)	Letter responsive to FDA request, initial advertising for Claritin (loratadine) 10 mg Tablets was submitted.
8/10/89	Letter submitting material and data to amend submission of 8/14/85.
8/16/89 (N)	Updated loratadine package insert submitted as requested in a 8/15/89 telephone conversation with FDA.
8/21/89 (N)	As requested by FDA in 8/15 and 8/18/89 telephone conversations letter sent to FDA

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	resubmitting data regarding studies C88-053-01 and C85-067-01 originally submitted on 4/24/89.
8/23/89 (N)	As requested by FDA in a 8/22/89 telephone conversation, letter to FDA resubmitting. Product Information Sheet included in our 8/1/89 submission.
8/24/89 (N)	Internal memo summarizing 8/24/89 telephone conversation with FDA wherein solubility of loratadine in water was provided.
8/29/89 (N)	As requested by FDA in a 8/28/89 telephone conversation, letter to FDA resubmitting volumes 1.57 to 1.62 of NDA submitted 10/31/86 and Vol. 1 of our 11/23/88 submission.
9/6/89 (N)	Per FDA request by C. Ledet, copies of loratadine package inserts for some of the foreign countries where loratadine is marketed were submitted.
9/6/89 (N)	As requested by Dr. P. Hepp of FDA in 8/15/89 and 8/18/89 telephone conversations, data concerning clinical studies C88-053-01; C85-067-01 and C88-047 submitted.
9/13/89 (N)	Responsive to FDA telephone calls of 9/11 and 9/12/89, letter sent enclosing our 12/21/89 submission to Swedish HR file.
9/18/89	FDA letter commenting on our submissions of 5/4, 5/5/ and 5/10/89.
10/11/89 (N)	FDA letter commenting on initial advertising for Claritin Tablets submitted 8/4/89.
10/12/89	Internal memo summarizing a 10/12/89 telephone call with Dr. Burke of FDA.
10/27/89 (N)	Internal memo summarizing 10/27/89 telephone conversation with Dr. Burke of FDA regarding labeling issue: Tumorigenesis.
11/8/89 (N)	Animal tumor data resubmitted as requested by Dr. Coulter of FDA.
11/16/89 (N)	Meeting with FDA regarding loratadine carcinogenicity studies.
12/5/89 (N)	Minutes of FDA meeting of 11/16/89 submitted to FDA regarding loratadine carcinogenicity studies. We also submitted comments from Dr. Zbinden of Switzerland on studies P-5407 and P-5340 and his CV as well as a revised loratadine package insert.
12/13/89 (N)	Per request by Dr. Coulter (FDA), we submitted new data and resubmitted carcinogenicity/mutagenicity documents of 11/8/89 and 12/5/89.
12/22/89 (N)	A full explanation of toxicological data (P-5155) and statistical analysis of 10/31/89

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	submitted in response to 12/17/89 phone conversation with Dr. Coulter (FDA).
1/22/90 (N)	Corrected minutes of 11/16/89 meeting with FDA regarding carcinogenicity studies to replace minutes submitted 12/5/89.
2/26/90	Annual report for loratadine Tablets submitted.
3/22/90 (N)	Submitted record of phone conversation of 3/9/90 between Dr. Perry and Dr. Coulter (FDA) regarding toxicology/pathology questions on loratadine carcinogenicity studies.
3/23/90 (N)	FDA letter summarizing 3/9/90 telephone conversation between Drs. Perry and Coulter regarding loratadine carcinogenicity studies.
4/23/90 (N)	As requested by Dr. Straus (FDA), we enclosed five adverse reaction reports previously submitted on 7/26/89 as part of loratadine Safety update.
5/21/90 (N)	As requested by Dr. Straus (FDA), confidence intervals for our major NDA clinical studies were submitted.
6/4/90 (N)	Letter to FDA withdrawing the alternate AMF process for tablet manufacture in response to comments by FDA investigators during pre-NDA inspection of 4-6-90 to 5-15-90.
6/19/90 (N)	Responsive to the FDA letter of 3/23/90 and 3/9/90 telephone conversation between Drs. Perry and Coulter concerning carcinogenicity studies, we submitted 16 copies of responses including justification for selection of doses used in rat, pathology working group (PWG) reports in CD-1 mice and sprague dawley rats, hepatic hismorphologic changes in rats, and effect of loratadine on mouse (liver drug metabolism enzymes).
7/9/90	New protocol and name and CV of new investigator submitted.
8/16/90	Internal memo summarizing a 8/16/90 telephone conversation with C. Ledet (FDA) regarding efficacy data.
8/27/90 (N)	As requested by Dr. Taylor (FDA) on 7/31/90, we submitted comparative (animals vs humans) pharmacokinetic data; P-5085 and P-5106.
9/10/90 (N)	Replacement page for one submitted 8/27/90 was sent to FDA.
9/18/90 (N)	Confirming a 9/18/90 telephone call, we requested Dr. Temple's involvement in facilitating completion of NDA review and requested meeting on adequacy of carcinogenicity data. Provided expert scientists; Drs. Zbinden, Williams, Wagner, and Busnick as a resource for the meeting.

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9/24/90 (N)	Internal Memo summarizing 9/24/90 telephone conversation between Dr. Given and Dr. Temple (FDA) - request of 9/18/90 for meeting denied. loratadine will be discussed at next available carcinogenicity assessment committee (CAC) meeting.
10/2/90 (N)	Internal memo summarizing 10/2/90 telephone conversation with C. Ledet of FDA regarding our proposed submission to our NDA (carcinogenicity data).
10/3/90 (N)	Letter to Dr. Burke of FDA requesting meeting to facilitate review and approval of loratadine NDA; we also submitted expert reports, assessment of PWG review of tumor pathology, comments on dose selection (MTD), package insert sections from NCEs approved since 1980 with hepatic and non-hepatic tumors noted in the labeling.
10/15/90 (N)	Internal memo summarizing telephone calls to FDA on 10/9, 10/10 and 10/12/90 regarding our 10/3/90 submission.
10/16/90 (N)	Internal memo summarizing 10/16/90 telephone conversation between Dr.Given and Dr. Burke (FDA) regarding our 10/3/90 submission.
10/18/90 (N)	Proposed loratadine labeling for Carcinogenesis, Mutagenesis, and Impairment of Fertility sections submitted in response to FDA's telephone request by Dr. Burke of 10/16/90 - two versions sent which differ in degree of detail.
11/1/90 (N)	Pursuant to a 11/1/90 FDA telephone request from C. Ledet, we submitted five addition copies of material submitted on 10/18/90.
11/2/90 (N)	Telephone conversation: between Dr. Perry and Dr. Contrera (CAC chairman): CAC met to discuss loratadine; conclusions will be forwarded to the Division (Dr. Burke) and will be communicated to Schering. Conclusions stated that mouse carcinogenicity study did not reach MTD and that the oncology studies in mouse were positive but equivocal in rat. It was also stated that loratadine is an enzyme inducer somewhat comparable to phenobarbital.
12/6/90 (N)	Telefax from FDA to Dr. Perry summarizing comments from Biopharm review of our amendments dated 8/3/ and 9/6/89.
12/14/90 (N)	Internal memo summarizing 12/14/90 telephone conversation with a Dr. Palva (Finland) regarding loratadine toxicology.
1/2/91	Two preclinical loratadine Pharmacology/Toxicology reports submitted.
1/10/91	Annual Report for loratadine Tablets submitted.

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1/29/91 (N)	Pursuant to a 1/25/91 telephone request by C. Ledet of FDA, we submitted five additional copies of our 10/3/90 submission.
3/28/91 (N)	Seven reports regarding loratadine submitted.
4/23/91 (N)	Internal memo summarizing 4/23/91 telephone conversation between Dr. Given and C. Ledet (FDA) regarding scheduling a loratadine pre-Advisory Committee meeting at FDA.
5/1/91 (N)	Internal memo summarizing 5/1/91 telephone conversation: Meeting with FDA (Pre Advisory Committee) has been confirmed for Thursday, May 23, 1991, 12 to 1 PM Parklawn Building Conference Room I.
5/8/91 (N)	Letter from Dr. Burke of FDA, regarding agenda for upcoming Advisory Committee meeting scheduled for June 13 and 14, 1991. Requested our agenda and summary of carcinogenicity data on loratadine to be sent to Ms. Debbie Yaplee. Also confirmed our meeting with FDA on May 23, 1991 from 12 to 1 PM.
5/15/91 (N)	Letter to Ms. D. Yaplee of FDA: Agenda for pre-meeting on 5/23/91 regarding upcoming Pulmonary-Allergy Drug Product Advisory Committee meeting.
5/23/91 (N)	Letter to Dr. Burke of FDA: Submitted Review Book for Pulmonary-Allergy Drug Products Advisory Committee meeting planned on June 13 and 14, 1991.
5/24/91 (N)	Internal memo summarizing telephone conversation: with FDA regarding Minutes of 5/23/91 Pre-Meeting of Advisory Committee.
5/28/91 (N)	Letter to Dr. Burke of FDA, we amended NDA by submitting several reports including: 1. Evaluation of the Experimental Data for Loratadine (Shipp report). 2. Evaluation on an Inducer of Liver. Microsomal Cytochrome P450 in Rats and Mice. 3. A summary of the Epidermal Evidence on the Carcinogenicity of Phenobarbital.
6/6/91	Letter to Dr. Burke of FDA enclosing Amendment to Annual Report on loratadine submitted on 1/10/91.
6/6/91 (N)	Letter to Dr. Burke of FDA: Revised pages for those previously submitted 5/23/91 - loratadine Overview Section for Advisory Committee Review Book.
6/26/91 (N)	Internal memo summarizing 6/26/91 telephone conversation regarding presentation slides, agenda, and questions and answers from Pulmonary-Allergy Advisory Committee meeting of June 13 and 14, 1991.
6/28/91 (N)	Internal memo summarizing 6/28/91 telephone conversation with Sue Johnson, Medical

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	Officer request copies of loratadine study reports C85-013-01 and M85-706A.
7/3/91 (N)	Letter to Dr. Burke of FDA: Request made for meeting with FDA personnel to identify next steps Re: Approval of loratadine tabs pursuant to recent Pulmonary-Allergy Drug Advisory Committee held June 13 and 14, 1991.
7/8/91 (N)	Internal memo summarizing two separate 7/8/91 telephone conversations with Ms. Schumaker and C. Ledet of FDA regarding format for: loratadine/434 Safety Updates.
7/9/91 (N)	Letter to FDA: As discussed in 7/8/91 telephone conversation, the desk copy of Study Reports M85-706A and C85-013-01 sent to Sue Johnson. These Study Reports were previously submitted in original NDA (10-31-86).
7/17/91 (N)	Internal memo summarizing 7/17/91 telephone conversation: Discussion with Conrad Ledet on what is required from both Dr. Burke and Dr. Straus for the loratadine Safety Update.
7/19/91 (N) and 7/26/91 (N)	Internal memo summarizing two telephone conversations on 7/19 and 7/26/91: Discussions with Dr. Straus to determine what is required for the loratadine Safety Update.
7/26/91 (N)	Letter to Dr. Burke of FDA. Listing what will be included in the updated Safety Overview. (Reference our telephone conversations on 7/17, 7/19, 7/22 and 7/23/91)
8/7/91 (N)	Letter to FDA: Submission to Dr. Straus of these electronic data bases which he has requested.
8/7/91 (N) and 8/8/91 (N)	Internal memo summarizing two telephone conversations on 7/7 and 7/8/91: Discussions with Dr. Straus who requested an additional data base disk and listing on the Safety Data.
8/12/91 (N)	Letter to Dr. Straus of FDA: Submission of two additional disks containing Safety Data.
8/13/91 (N)	Internal memo summarizing 8/13/91 telephone conversation regarding request from Dr. Straus (FDA) for a modified disk on ADR dates.
8/14/91 (N)	Internal memo summarizing 8/14/91 telephone conversation with Dr. Taylor, Supervisor Pharmacologist. He agreed that we could submit toxicology reports to the IND and then reference them in the PI.
8/19/91	Letter to Dr. Burke of FDA enclosing three loratadine toxicology reports.
8/23/91 (N)	Letter to FDA: Revised Package Insert submission - Safety Update includes both NDA data and information completed since NDA

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	filing (Data cutoff date 6/30/91). Supersedes Safety Update of 7/89 - Volumes 3 to 23 includes copies of case report forms on patients in controlled studies who discontinued due to adverse events.
8/23/91 (N)	Internal memo summarizing a 8/23/91 telephone conversation with C. Ledet (FDA) who called to refer a message from Dr. Straus. Dr. Straus requested CRF's for patients with ADR's of anxiety, dermatitis and hypertension.
8/26/91 (N)	Letter to Dr. Straus of FDA, listing of patients experiencing myalgia and their SGOT data sent to Dr. Straus, per his request - CPK data was not collected in controlled clinical studies and there was very little LDH data - so we were unable to send this additional data.
8/27/91 (N)	Internal memo summarizing a 8/27/91 telephone conversation with FDA request from Dr. Straus for labelling on disk and information concerning IND 3253.
8/28/91 (N)	Letter to FDA, disk sent to Dr. Straus containing CLARITIN™ tablet package insert (labelling) which was included in the 8/21/91 Safety Update Submission.
8/29/91 (N)	Letter to FDA: Two 3½ inch high density disks sent to Dr. Straus, per his request on 8/28/91, one data file contained corrected version of dropouts for adverse experiences he already had, the other one was a summary of all adverse experiences reported in controlled clinical trials with loratadine.
8/29/91 (N)	Internal memo summarizing a 8/29/91 telephone conversation with C. Ledet of FDA who relayed three additional requests from Dr. Straus. 1. List of all studies submitted to NDA. 2. List of <u>all</u> other studies submitted worldwide not in (1). 3. CRF's for withdrawal due to ADR's.
9/5/91 (N)	Internal memo summarizing a 9/5/91 telephone conversation: C. Ledet requesting additional CRF's and copy of labeling and 1st Volume of 1991 Safety update.
9/11/91 (N)	Internal memo summarizing a 9/11/91 telephone conversation: Additional requests from Dr. Straus.
9/12/91 (N)	Letter to Dr. Straus of FDA: Floppy disk on CLARITIN™ Package Insert sent to Dr. Straus, per his request.
9/13/91 (N)	Letter to Dr. Burke FDA: Responsive to Dr. Straus' request, case report forms were submitted for patients who had elevations of SGOT's form baseline.

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9/19/91 (N)	Letter to Dr. Straus of FDA: 2 Diskettes submitted each containing one file summarizing ADR reported by patients discontinuing for adverse experiences (DC-AE4). List of variables and their definitions also included.
9/19/91 (N)	Internal memo summarizing a 9/19/91 telephone conversation with C. Ledet of FDA regarding Labeling meeting planned for 9/26/91.
9/24/91 (N)	Internal memo summarizing a 9/24/91 telephone conversation with C. Ledet: Requests from Dr. Straus on loratadine dropouts and from Dr. Burke for summaries.
10/3/91 (N)	Internal memo summarizing a 10/3/91 telephone conversation with C. Ledet (FDA) regarding status of labeling meeting. Dr. Straus had some questions regarding myalgia data with SGOT and SGPT levels. We will send C. Ledet a list of these patients. Dr. Giaquinto will meet with Dr. Burke (FDA) 10-17-91 regarding studies included in Appendix XV of Safety Update. Internal meeting at FDA 10/31/91 regarding clinical aspects of NDA.
10/4/91 (N)	Letter to Dr. Burke of FDA: As requested by Dr. Sherwin Straus (FDA) we submitted a list of patients who experienced myalgia along with their SGOT data. CPK data was not collected in our controlled clinical trials and there was no LDH data reported by patients experiencing myalgia.
10/9/91 (N)	Internal memo summarizing a 10/9/91 telephone conversation with Dr. Poochikian Re: Commitment on origin impurities. Information had been submitted to Sch 434 NDA, not to loratadine. Dr. Poochikian said it was not necessary to submit to loratadine NDA as it had been sent to Sch 434 NDA. He also said "origin impurities" only, chemistry commitment or deficiency he knew of. We will follow-up on a FAX sent in March 1990 to see if response had been made.
10/10/91 (N)	Internal memo summarizing a 10/10/91 telephone conversation with C. Ledet (FDA) requesting clarification of data set ARL-ADR sent to Dr. Straus.
10/15/91 (N)	Internal memo summarizing a 10/15/91 telephone conversation with C. Ledet confirmed status of these Faxes 3/22/90 and 12/6/90.
10/16/91 (N)	Letter to Dr. Burke of FDA: Submitted 12 copies of final printed labeling to FDA for CLARITIN® tablets.
10/16/91 (N)	Internal memo summarizing a 10/16/91 telephone conversation with C. Ledet: Additional requests from Dr. Straus concerning labelling and data set files.

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10/16/91 (N)	Letter to Dr. Burke of FDA: In response to C. Ledet's telephone request of 9/24/91, we submitted additional data; number and frequency of adverse events; SAS data set with variables. PAT #ETC; all adverse experiences; follow-up on 89-05-020 and 8-06-05I; additional lab data; variable definitions-2 diskettes submitted from Dr. Straus.
10/17/91 (N)	Telefax from C. Ledet of FDA listing study numbers included in SAS data set files.
10/17/91 (N)	Internal memo summarizing a 10/17/91 telephone conversation with C. Ledet re-sending a 3/28/90 FAX concerning chemistry deficiencies and also a request to identify study types.
10/20/91 (N)	Letter to Dr. Burke of FDA: Responsive to a 10/20/91 telephone request by C. Ledet, we submitted our comments to the chemistry reviewer's questions.
10/21/91 (N)	Internal memo summarizing a 10/21/91 telephone conversation with C. Ledet. 10/17/91 telefaxed copy from C. Ledet (FDA) for study numbers included in SAS data set files. Dr. Straus would like to know which studies were randomized and placebo controlled. Response to FDA should be faxed to them and followed-up in writing.
10/21/91 (N)	Internal memo summarizing a 10/21/91 telephone conversation with C. Ledet who confirmed additional request from Dr. Straus Re: Safety Update.
10/22/91 (N)	Letter to FDA: Response to FAX from C. Ledet (FDA) of 10/17/91 regarding randomized and placebo controlled studies in SAS data set file sent to Dr. Straus 8/7/91. List of controlled studies also sent.
10/23/91 (N)	Internal memo summarizing a 10/23/91 telephone conversation regarding request from Dr. Burke, FDA of list of counties where loratadine was either not approved, or withdrawn and reasons.
10/24/91 (N)	Internal memo summarizing a 10/24/91 telephone conversation regarding additional request from Dr. Straus Re: loratadine ADR files, Proc. Freq. SAS output.
10/24/91 (N)	Internal memo summarizing a 10/24/91 telephone conversation regarding comments from C. Ledet on revision to the labeling to include biopharm information.
10/25/91 (N)	Letter to Dr. Burke of FDA: responsive to a request by C. Ledet, we submitted updated summary basis of approval; included toxicology information as well as safety information from the Safety Update submitted August 1991.

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10/25/91 (N)	Internal memo summarizing a 10/25/91 telephone conversation with Dr. Burke of FDA clarifying that efficacy; summaries need to be included in Appendix XV and that Finland was the only country where the loratadine tablet application was withdrawn.
10/29/91 (N)	Internal memo summarizing a 10/29/91 telephone conversation with C. Ledet (FDA) who called to inform us that 10/31 meeting was canceled and they will be scheduling a meeting with us to discuss liver toxicity.
10/30/91 (N)	Letter to Dr. Burke of FDA: as discussed with Dr. Poochikian on 10/22/91, we sent a request for extension of the loratadine Tablets expiration date from 30 months to 36 months. Submitted real time data on production batches from tablets manufactured by the Glatt Process.
11/04/91 (N)	Letter to Dr. Burke of FDA: responsive to request by C. Ledet, we submitted Foreign labeling for CLARITIN™ tablets submitted to NDA.
11/04/91 (N)	Internal memo summarizing 11/4/91 telephone conversation with C. Ledet (FDA) who called to determine if a date had been set up to meet, not date as yet, currently formulating questions/issues they want addressed. Dr. Straus also wanted inferential analysis of difference between QTC and QRS on loratadine and placebo. Case reports for overdoses, define right and hypertrophy and results of Study C83-033-01 on a disk SDD file.
11/13/91 (N)	Internal memo summarizing a 11/13/91 telephone conversation with Dr. Straus who had additional requests; list of studies which had LFT determinations. Additional values; treatment, post-treatment. He found an old review on Study C-83-033-01, so we can hold sending data file for the time being.
11/14/91 (N)	Internal memo summarizing a 11/14/91 telephone conversation regarding request from Dr. Burke on Hepatic failure case from Inman's study (UK).
11/15/91 (N)	Internal memo summarizing a 11/15/91 telephone conversation with called Dr. Poochikian (FDA) who called regarding our request for 36 month expiration dating for loratadine, he had a few questions that needed to be answered prior to extending date such as stability protocol clarification and other issues. Letter regarding this has been signed by him.
11/15/91 (N)	FAX Letter from Dr. Poochikian of FDA: Providing comments on our amendments dated 8/21/91, 10/16/91, 10/25/91 and 10/30/91 regarding manufacturing and controls and stating FDA records show that the following documents previously requested are still

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	required: 2 regulatory ID tests for Drug product, impurities, amended spec sheet and method, amended stability protocol, further data on validation testing; Re: 8/21/91 package insert "Description" and "How Supplied" needed to be modified; 10/31/91 amendment for extending expiration date to 36 months, stability data questions; EA for Irish Fine Chemicals should be obtained.
11/18/91 (N)	Letter to Dr. Burke of FDA: As requested by Dr. Burke we submitted efficacy summaries for each study contained in Appendix XV of August 1991 Safety Update.
12/2/91 (N)	Letter to Dr. Burke of FDA: As requested by Drs. Straus and Burke in a 10/29/91 telephone call, we submitted patient exposure from all loratadine dosage forms, SGOT and SGPT information and other liver function analysis.
12/3/91 (N)	Internal memo summarizing 12/3/91 telephone conversation with Dr. Poochikian of FDA regarding loratadine tablet storage temperature and expiration date.
12/3/91 (N)	Internal memo summarizing 12/4/91 telephone conversation with Dr. Burke of FDA regarding additional information on adverse events and living effect information.
12/4/91 (N)	Letter to Dr. Burke of FDA enclosing (per request of C. Ledet of FDA) additional copy of Vol. 1.30 for loratadine Tablets originally submitted with NDA on 10/31/86.
12/4/91 (N)	Telephone conference with Dr. Burke of FDA regarding numerous requests for loratadine Studies (See 12/11/91 letter to FDA).
12/9/91 (N)	Letter to Dr. Burke of FDA: responsive to 12/21 and 10/21/91 telephone requests by C. Ledet, we submitted additional information on five hepatic reactions, spontaneous reports as well as location of major clinical studies as requested by C. Ledet in 10/21 and 10/24/91 telephone calls.
12/11/91 (N)	Letter to Dr. Burke of FDA: Submitted patient exposure information to loratadine by indication, provided list of controlled studies, lists of deaths, drop-outs and spontaneous reports, and also providing hepatic information on loratadine, terfenadine and astemizole per 12/4/91 telephone conference with Dr. Burke of FDA and discussion with Dr. Giaquinto of Schering on 12/10/91.
12/18/91 (N)	Letter to Dr. Burke of FDA: Submitted response to 11/15/91 FDA letter from Dr. Poochikian concerning chemistry information.

Document Date*	Comment
12/19/91 (N)	Letter to Drug Master File Staff of FDA as requested in FDA letter of 11/15/91 we updated Type II DMF6626, loratadine.
12/20/91 (N)	Letter to Dr. Burke of FDA: Submitted additional SGOT data from Sch 434 study and analysis of QRS and PR intervals as requested by FDA in 11/4/91 telephone conversation.
12/23/91 (N)	Letter to Dr. Burke of FDA: Submitted information concerning mouse lymphoma data showing loratadine is safe product.
1/3/92 (N)	Letter Dr. Burke of FDA: We resubmitted full copies of References 1, 4, and 6 of 12/23/91 submission to FDA; some pages in 12/23/91 submission were missing.
1/29/92 (N)	Internal memo by Dr. Giaquinto regarding his 12/29/92 telephone conversations with FDA: regarding FDA Inside Agency meeting scheduled for 4/92 with Drs. Burlington, Peck and Burke regarding status of loratadine review.
1/29/92 (N)	Letter to Dr. Burke of FDA enclosing Annual Report for loratadine Tablets.
3/6/92 (N)	Internal memo summarizing a 3/6/91 telephone conversation: our Ms. B. Matlosz spoke with Dr. Poochikian regarding requirements for manufacturing site change for loratadine tablets. He listed requirements which included an inspection needed of manufacturing site.
3/12/91 (N)	Internal memo summarizing a 3/12/91 telephone conversation: between B. Matlosz and Dr. Leak who called regarding unit packaging (blister pak). After talking to Marketing, called Dr. Leak and told him this was a "one shot" deal to each pharmacy nationwide. Dr. Leak requested manufacturing and expiration dates.
3/13/92 (N)	Internal memo summarizing a 3/13/92 telephone by Ms. B. Matlosz who provided Dr. Leak with information he requested on 3/12/92.
3/18/92 (N)	Letter to Dr. Burke of FDA: Submitted two hard diskettes in response to Dr. Lin's 2/20/92 telephone request for preclinical study data which included code sheets and a printout of data.
3/18/92 (N) and 3/19/92 (N)	Internal memo summarizing a 3/18/92 telephone conversation with Dr. Lin who called to discuss statistical data analysis in Table 3 and 4 of 5/27/91 submission. Internal memo also summarizing 3/19/92 telephone conference call with Dr. Lin who requested additional data.
3/25/92 (N)	Letter to Dr. Burke of FDA: Briefing materials sent to Drs. Burke, Peck and Temple for FDA 4/22/92 meeting to discuss loratadine Tablet NDA.

Document Date*	Comment
3/27/92 (N)	Letter to Dr. S. Schenkin of the University of Texas regarding 4/22/92 meeting with FDA concerning loratadine Tablet NDA in Dr. Perk's FDA office.
4/8/92 (N)	Letter to Dr. Burke of FDA: We submitted to loratadine IND and NDA manuscript and statistical report for study I88-317 conducted in Canada.
4/9/92 (N)	Letter to FDA: Desk copy of briefing materials (previously submitted to FDA on 3/25/92) for FDA 4/22/92 meeting sent to Dr. Burlington (Deputy Director).
4/14/92 (N)	Internal memo summarizing 4/14/92 telephone conversation with Dr. Lin who called to verify that after FDA Administration meeting that FDA did not feel a meeting on biostatistical issues was necessary.
5/11/92 (N)	Internal memo summarizing a 5/11/92 telephone conversation with Dr. Lin of FDA Biometrics Division regarding specifics on their analysis methodology; statistician on vacation.
5/12/92 (N)	Internal memo summarizing a telephone conversation with Drs. Ali and Schuirman of FDA Biometrics who called to discuss the analysis methodology.
5/12/92 (N)	Internal memo summarizing 5/12/92 telephone conversation with C. Ledet of FDA regarding contact in FDA Biometrics Division in Dr. Lin's absence.
5/14/92 (N)	Meeting with FDA regarding loratadine tablet NDA.
5/15/92 (N)	Three letters to three FDA officials: we submitted sets of the Schering presentation slides used at 5/14/92 meeting with FDA. Also included a publication on an enzyme induction study.
5/18/92 (N)	Internal memo summarizing minutes of 5/14/92 FDA meeting.
5/27/92 (N)	FAX letter to FDA: Pages containing loratadine manufacturing sites listed in original NDA (10/31/86) were sent to Ms. Schumaker (per her request).
6/29/92 (N)	Letter to Dr. Burke of FDA: We provided preclinical information in support of loratadine NDA to address points discussed at FDA 5/14/92 meeting.
7/1/92 (N)	Letter to Dr. Burke of FDA: We submitted additional mutagenicity information in support of loratadine NDA to address points discussed in a 6/18/92 telephone conversation with Dr. Taylor.
7/20/92 (N)	Telephone conversation with Dr. Burke of FDA regarding repeat AMES mutagenicity assay.

Document Date*	Comment
7/27/92 (N)	Letter to FDA: We enclosed final protocol which is being used in the repeat AMES mutagenicity assay sent to FDA. Study started 7/27/92 and final report should be available 9/92.
8/6/92 (N)	Letter from Dr. Burke who provided comments from FDA on our 12/18/91 amendment regarding stability for alternate blister packaging; additional information requested.
8/20/92 (N)	Letter to Dr. Burke of FDA: Results of repeat mutagenicity assay submitted, as requested by FDA in a 7/20/92 telephone conversation.
8/26/92 (N)	Letter to Dr. Burke enclosing: Responses to his 8/6/92 FDA letter regarding manufacturing and controls information.
8/28/92 (N)	Letter: As requested by C. Ledet, submitted a copy of Volumes 1.33, 1.34 and 1.35 of the original NDA (10/31/86) for review of the biopharm data.
9/2/92 (N)	Meeting with Schering and FDA personnel regarding safety update and, SBA launch advertising for loratadine tablets.
9/8/92	Internal memo summarizing minutes of loratadine FDA/Schering meeting on 9/2/92.
9/8/92 (N)	Letter: As requested by C. Ledet, we submitted a desk copy of study C88-053 which had been submitted 8/16/88.
9/11/92 (N)	Letter to Dr. Burke of FDA: As requested at FDA 9/2/92 meeting, submitted Safety Update with cutoff date of 5/31/92.
9/17/92 (N)	Letter: As requested in FDA 9/2/92 meeting, submitted introductory advertising pieces for CLARITIN Tablets for FDA review.
9/18/92 (N)	Internal memo summarizing 9/18/92 telephone conversation with C. Ledet (FDA) who called to request that we verify that clinical studies C84-008, C84-111, C85--027, and I84-317 were pivotal studies. After reviewing the NDA, we were able to verify this. He also asked that we provide additional information on pediatric experience with loratadine. We agreed to provide that information.
9/21/92 (N)	Internal memo summarizing 9/21/92 telephone conversation with C. Ledet of FDA to discuss the pediatric information which he requested on 9/18/92; referred him to our 12/11/91 submission.
9/23/92 (N)	Internal memo summarizing a 9/23/92 telephone conversation with C. Ledet of FDA to inquire if given the apparent progress on the loratadine submission if there would any difficulty in our running "coming soon" ads around a 11/92 timeframe. He suggested that

Document Date*	Comment
	we call the Drug Advertising Division for a decision.
9/25/92 (N)	Internal memo summarizing 9/25/92 telephone conversation with the Drug Advertising Division regarding running the "coming soon" ads in 11/92. She inquired as to whether we expected a black box warning; we do not. She said she would be happy to look at the proposed ad. We FAXed a copy to her.
9/28/92 (N)	Internal memo summarizing a 9/28/92 telephone conversation with C. Ledet who called relaying additional information for the Pharmacology review on our 8/20/92 submission. Asked that we include the final study report when we submit our comments.
10/5/92 (N)	Internal memo summarizing 10/5/92 telephone conversation with C. Ledet of FDA who called to relay ten specific requests from Dr. Burke inter alia foreign labeling changes, any foreign regulatory action such as market withdrawals, information regarding serious adverse reaction due to loratadine use alone or in combination with, e.g., ketoconazole.
10/7/92 (N)	Letter to Dr. Burke of FDA: As requested by C. Ledet, we submitted the final mutagenicity study report; data tables for this study were submitted on 8/20/92. We also submitted a discussion of the results of cytotoxicity reported in this study and the original mutagenicity study.
10/9/92 (N)	Letter to Dr. Burke of FDA: In response to telephone requests of 10/5/92 and 10/6/92, we submitted additional information on new foreign labeling since 11/4/91, anything related to safety in foreign labeling, any foreign regulatory actions, adverse event information they are not aware of for loratadine or loratadine "D", list of selected adverse events, number of patients receiving loratadine, adverse events information for seasonal allergic rhinitis and perennial allergic rhinitis, and information for two patients treated with terfenadine.
10/13/92 (N)	Internal memo summarizing a 10/13/92 telephone conversation with Dr. Hossain on protocol C91-339-01.
10/15/92 (N)	Letter from W.F. Rumble of FDA commenting on our submission dated 9/17/92 of introductory advertising materials for Claritin Tablets.
10/20/92 (N)	Internal memo summarizing a 10/20/92 telephone conversation with C. Ledet of FDA who said the chemistry reviewer had two requests for information: 1. Provide modified blister backing for 10 unit dose; and 2. Amend page 4 of the August 26, 1992 Amendment to indicate change made by a December 18, 1991 amendment.

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10/20/92 (N)	Letter to Dr. Burke of FDA, we submitted our responses to chemistry reviewer's comments as requested by C. Ledet in a 10/20/92 telephone conversation.
10/23/92 (N)	Letter to W.F. Rumble of FDA in response to his 10/15/92 letter regarding our advertising submission; and a 10/21/92 telephone conversation between Schering and FDA people wherein an appropriate response was agreed upon. We submitted a synopsis and pertinent Tables form studies to support claims in an comment 1 and responded to the other comments.
11/12/92 (N)	Internal memo summarizing a 11/12/92 telephone conversation with C. Ledet of FDA regarding status of review of Claritin package insert and labelling.
11/12/92 (N)	Internal memo summarizing a 11/12/92 telephone conversation with Dr. Rumble of FDA regarding Claritin advertising review.
11/16/92 (N)	Internal memo summarizing a 11/16/92 telephone conversation with C. Ledet of FDA regarding Claritin review of labelling and package insert. Drs. Burke and Leak have submitted three post-approval commitments for incorporation into the labelling. C. Ledet promised to submit a revised draft package insert incorporation these changes.
11/18/92 (N)	Letter to Dr. Burke of FDA in response to C. Ledet's telephone call and fax of 11/16/92: we resubmitted a revised package insert submitted 9/11/92.
11/19/92 (N)	Internal memo summarizing a 11/19/92 telephone conversation with C. Ledet of FDA regarding status of our 11/18/92 response which was received on 11/19/92 at 7:30 am in the mailroom. We asked Mr. C. Ledet to leave a message for Dr. Burke that we wanted to call him.
11/19/92 (N)	Internal memo summarizing a 11/19/92 telephone conversation with C. Ledet who called to confirm the receive our 11/18/92 letter and would call next monday.
11/24/92 (N)	Internal memo summarizing a 11/24/92 telephone conversation between Dr. Giaquinto of Schering and Dr. Burke of FDA regarding revisions in Claritin package insert and requested addition 8 sets of color slides from material submitted 11/18/92.
11/24/92 (N)	Letter to Dr. Burke of FDA we submitted color slides sets he requested.
11/25/92 (N)	Letter to Dr. Burke of FDA in response to his 11/25/92 telephone call wherein he requested changes in our draft package insert, we submitted revise final draft incorporating all revisions.

Document Date*	Comment
11/30/92 (N)	Internal memo summarizing a 11/30/92 telephone conversation with W. Rumble of FDA regarding claritin advertising review in progress.
11/30/92	Letter to Dr. Burke of FDA, revised loratadine labelling sent.
12/2/92 (N)	Internal memo summarizing a 12/2/92 telephone conversation with C. Ledet of FDA regarding Claritin package insert review in progress.
12/7/92 (N)	Internal memo summarizing a 12/7/92 telephone conversation with W. Rumble of FDA regarding Claritin advertising review in progress.
12/9/92 (N)	Internal memo summarizing a 12/9/92 telephone conversation with C. Ledet of FDA who called regarding two additional changes in 11/31/92 labelling requested by Dr. Burke. These charges were discussed with inter alia Dr. Giaquinto of Schering and we called to so inform FDA. FDA will include this approval in forthcoming letter on labelling.
12/9/92 (N)	Internal memo summarizing a 12/9/92 telephone call to W. Rumble of FDA regarding status of Claritin advertising review. Mr. Rumble promised to fax copy of soon to be issued letter from Dr. Burke on this matter.
12/10/92 (N)	Letter to Dr. Burke of FDA sent in response to Ms. Schumaker's fax dated 12/9/92 regarding deficiencies in our Environmental Assessment (EA) for Claritin Tablets. We submitted a revised EA after approval of Claritin NDA.
12/11/92 (N)	Internal memo summarizing a 12/11/92 telephone conversation with Ms. C. Schumaker of FDA concerning our Claritin EA letter dated 12/10/92. Ms. Schumaker requested that we revise the letter to promise a revised EA would be submitted on a specific date, e.g., 3 months after NDA approval. We agreed to do this.
12/11/92 (N)	Telefax letter to Ms. C. Schumaker concerning Claritin EA which includes statement she requested in our 12/11/92 telephone conversation and a request by us to destroy the 12/10/92 letter.
12/14/92 (N)	Internal memo summarizing a 12/14/92 telephone call to C. Ledet of FDA regarding status of the Claritin NDA review; C. Ledet said the package had not yet been sent to Dr. Temple for review.
12/16/92 (N)	Internal memo summarizing a 12/16/92 telephone conversation with C. Ledet of FDA regarding status of Claritin NDA review.
12/16/92 (N)	Internal memo summarizing a 12/16/92 telephone call from W. Rumble of FDA informing us that the Claritin advertising will need significant revisions.

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12/17/92 (N)	Internal memo summarizing a 12/17/92 telephone call with C. Ledet of FDA who stated that the status of the Claritin NDA review remained unchanged.
12/22/92 (N)	Internal memo summarizing a 12/22/2 telephone conversation with N. Drezen, Dr. M. Schreiber and W. Rumble regarding status of Claritin advertising review.
1/4/93 (N)	Internal memo summarizing a 1/4/92 telephone conversation with C. Ledet of FDA regarding status of Claritin NDA review update. NDA sent to Dr. Temple's office.
1/8/93 (N)	Internal memo summarizing a 1/8/93 telephone conversation with Linda Carter of FDA regarding status of Claritin NDA review by Dr. Temple.
1/8/93 (N)	Internal memo summarizing a 1/8/93 telephone conversation with Ken Feather and W. Rumble of FDA regarding FDA comments on Claritin advertising; a telephone conversation for 1/11/93 am was planned.
1/11/93 (N)	Letter from W. Rumble of FDA regarding Claritin introductory advertising materials submitted on 9/17/92 and 10/23/92 as well as the FDA letter dated 10/15/92; list of preliminary significant comments made.
1/12/93	Internal memo summarizing a 1/12/93 telephone conversation with W. Rumble and K. Feather of FDA regarding preliminary comments on Claritin advertising in W.Rumble's 1/11/93 letter. FDA agreed to meet us on 1/15/93 at FDA.
1/12/93	Letter to W. Rumble of FDA regarding comments he made in the 1/12/93 telephone conversation. Detail Aid in booklet form sent and the 1/15/93 meeting at FDA confirmed.
1/14/93 (N)	Internal memo summarizing a 1/14/93 telephone conversation with Dr. Vincent of FDA in which he requested the environment assessment for loratadine drug substance made at Irish Fine Chemicals, in a format releasable by Freedom of Information Act ("FOIA").
1/15/93 (N)	Letter to Dr. Burke of FDA enclosing the FOIA releasable Environmental Assessment for loratadine requested by Dr. Vincent on 1/14/93.
1/15/93 (N)	Meeting with FDA to discuss revisions in Claritin Advertising and W. Rumble's 1/11/93 letter.
1/19/93 (N)	Internal memo summarizing, 1/19/93 telephone conversation with L. Carter of FDA regarding status loratadine FOIA releasable environmental assessment and status of Dr. Temple's review of the loratadine NDA.

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1/21/93 (N)	Internal memo summarizing 1/21/93 telephone conversation with W. Rumble of FDA regarding status of FDA comments on Claritin advertising issues discussed at 1/15/93 meeting.
1/22/93 (N)	Internal memo summarizing 1/12/93 telephone call with Dr. Vincent of FDA regarding status of FDA review of loratadine FOIA EA.
1/25/93 (N)	Internal memo summarizing 1/25/93 telephone conversation with L. Carter of FDA regarding status of Dr. Temple's review of loratadine NDA.
1/26/93 (N)	Internal memo summarizing 1/26/93 telephone conversation with W. Rumble of FDA regarding loratadine advertising.
2/2/93 (N)	Letter from W. Rumble of FDA regarding loratadine Advertising.
2/3/93 (N)	Internal memo summarizing 2/3/93 telephone conversation with L. Carter of FDA regarding status of Dr. Temple's review of loratadine NDA.
2/5/93 (N)	Letter to W. Rumble of FDA in response to his 2/2/93 letter; we submitted revised loratadine advertising and detailed list of revisions made.
2/11/93 (N)	Letter from W. Rumble of FDA regarding comments on our revised loratadine advertising materials submitted on 2/5/93: materials accepted with proposed changes.
2/12/93 (N)	Letter to W. Rumble of FDA in response to his 2/11/93 letter; we submitted changes in response to 2/5/93 FDA letter.
2/17/93 (N)	Internal memo summarizing a 2/17/93 telephone call to L. Carter of FDA regarding status of Dr. Temple's review of loratadine NDA.
2/19/93	Letter to Dr. Burke of FDA submitting new clinical study protocol C92-258.
3/1/93 (N)	Letter from W. Rumble and Dr. Schreiber of FDA regarding loratadine advertising.
3/2/93 (N)	Internal memo summarizing 3/2/93 telephone conversation with W. Rumble and Dr. Schreiber of FDA regarding their 3/1/93 letter; we mutually agreed to revisions on loratadine advertising.
3/8/93 (N)	Letter to W. Rumble of FDA regarding their comments and our responses to the 3/1/93 letter and 3/2/93 telephone conversation concerning loratadine advertising concerning loratadine advertising; changes submitted regarding all issues outstanding.
3/12/93 (N)	Internal memo summarizing a 3/12/93 a.m. telephone conversation with C. Ledet of FDA

Document Date*	Comment
	regarding status of FDA review of loratadine NDA.
3/12/93 (N)	Internal memo summarizing a 3/12/93 p.m. telephone conversation with C. Ledet of FDA who called to relay some requests which were made in a 3/12/93 10:30 a.m. meeting with Dr. Burke.
3/17/93 (N)	Internal memo summarizing two separate telephone conversations with M. Ledet and Dr. Himmel, respectively, regarding requests by FDA for additional information.
3/17/93 (N)	Letter to Dr. Burke of FDA in response for additional information made 3/12/92 and 3/17/93; we submitted full copies of three clinical studies: C85-027; I84-317 and S88-047.
3/19/93 (N)	Internal memo summarizing 3/19/93 telephone conversation with Dr. Lin of FDA regarding status of Dr. Lin's statistical review of comments from Dr. Temple regarding loratadine.
3/22/93 (N)	Letter to Dr. Burke of FDA in response to items raised by C. Ledet of FDA in his 3/12/93 telephone conversation with Schering; we submitted a list of each of his requests followed by our responses thereto.
3/24/93 (N)	Internal memo summarizing a 3/24/93 telephone conversation with C. Ledet of FDA who called to inform us we should be receiving a package 3/24/93 containing information addressing all his requests made during the past week.
3/30/93 (N)	Internal memo summarizing 3/30/93 telephone conversation with C. Ledet of FDA regarding status of Dr. Temple's review of the loratadine NDA; we offered to send disk containing revised package insert for loratadine submitted November, 1992.
3/30/93 (N)	Letter to C. Ledet of FDA enclosing disk containing November, 1992 version of Claritin (loratadine) Tablets package insert as promised in our 3/30/93 telephone conversation.
4/1/93 (N)	Telefax from C. Ledet of FDA regarding change in loratadine package insert.
4/2/93 (N) and 4/6/93 (N)	Internal memo summarizing three telephone conversation with C. Ledet of FDA; two on 4/2/93 and one on 4/6/93 regarding revised package insert changes.
4/2/93 (N)	Letter to Dr. Burke of FDA enclosing revised package inserts proposed on 4/1/93 telefax and discussed in two 4/2/93 telephone conversations with C. Ledet.
4/6/93 (N)	Memo summarizing telephone call from C. Ledet of FDA informing us that the revised package insert went to Dr. Temple on 4/5/93.

Document Date*	Comment
4/7/93 (N)	Letter to Dr. Burke of FDA regarding November 18, 1992 letter from us regarding agreement to conduct interaction studies with erythromycin, ketoconazole and cimetidine post approval of loratadine tablets; outline of such interaction studies submitted and comments thereon submitted.
4/12/93 (N)	Telefax dated 4/12/93 from E. Coulter of FDA of the letter from Dr. Temple of FDA approving loratadine tablet NDA 19-658 as amended.
4/12/93 (N)	Letter to W. Rumble of FDA informing him that Dr. Temple has approved loratadine NDA and submitting proposed changes in loratadine advertising pieces discussed between parties over last several months.
4/13/93 (N)	Letter to Dr. Burke of FDA in response to requests in 4/12/93 NDA approval letter, we submitted 12 copies of the final printed labelling for loratadine.

(N) = Activities relating to New Drug Application 19-658. All other activities pertain to IND 21,249.

(D) = Drug Master File for loratadine.

* = All document date refer to dates of cover letters or dates of preparation of internal memo of telephone conversations, meetings or conference.

10238

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent No. 4,282,233

Inventor: Frank J. Villani and
Charles V. Magatti

Attn: Box Patent Ext.

Issue Date: August 4, 1981

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM

Honorable Commissioner of Patents and Trademarks
Washington, D. C. 20231

Sir:

Transmitted herewith for filing is an application for extension of term of U. S. Patent No. 4,282,233 and a duplicate of the papers thereof, certified as such.

Also submitted herewith is an additional original declaration for extension of U. S. Patent No. 4,282,233. Therefore, the present application is complete and entitled to a filing date of June 7, 1993.

Pursuant to the provisions of 37 C.F.R. §1.785(c), the undersigned appointed attorney for Applicant, Schering Corporation, states that Schering Corporation is the holder of the regulatory approval granted with respect to the regulatory review period for CLARITIN® (brand of loratadine) tablets as evidenced by (1) the submission on November 30, 1982 by Schering Corporation of IND #21,249 for loratadine (SCH 29851) oral capsules, a non-sedating antihistamine (see attached Exhibits III and IV); (2) the submission on October 31, 1986 by Schering Corporation of NDA #19-658 covering CLARITIN® (brand of loratadine) tablets, a non-sedating antihistamine for treatment of seasonal allergic rhinitis symptoms (see attached Exhibits V and VI); and (3) the FDA approval of Schering NDA #19-658 covering CLARITIN® (brand of loratadine) tablets for relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (see attached Exhibit VII).

The Commissioner is hereby authorized to charge payment in the amount of $1,000.00 and of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 19-0365. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Thomas D Hoffman

Thomas D. Hoffman
Registration No. 28,221
Attorney of Record for
Assignee of Record
Tel. No. (201) 822-7379

SCHERING-PLOUGH CORPORATION
Patent Department 3-West
One Giralda Farms
Madison, New Jersey 07940-1000

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